TO STUDY THE EFFICACY OF ORMILOXIFENE IN THE MEDICAL MANAGEMENT OF AUB

Dissertation submitted to

The Tamil Nadu Dr. MGR University,

Chennai

In partial fulfillment of the regulations

For the award of the degree of

M.S. OBSTETRICS AND GYNAECOLOGY

MADRAS MEDICAL COLLEGE

CHENNAI

APRIL 2017

CERTIFICATE

This is to certify that the dissertation entitled **"TO STUDY THE EFFICACY OF ORMILOXIFENE IN THE MEDICAL MANAGEMENT OF AUB"** submitted by **Dr.KANIMOZHI A** in the Institute of Social Obstetrics, Govt Kasturba Gandhi hospital (Madras Medical College) Triplicane , Chennai, in partial fulfillment of the university rules and regulations for award of MS degree in Obstetrics and Gynaecology under my guidance and supervision during the academic year 2014-2017.

Dr.M.K. Muralidharan, MS., MCH.,
Dean
Madras Medical College,
Chennai- 600 003

Prof.Dr.S.BabyVasumathi. MD.,DGO.,
Director and Superintendent
Institute of Obstetrics and Gynaecology,
Govt. Women and Children Hospital,
Madras Medical College,
Chennai – 600 005.

Prof. Dr. S.Vijaya .M.D., DGO.
Professor/ Director I/C
Institute of Social Obstetrics
Madras Medical College, Chennai-3

DECLARATION

I solemnly declare that this dissertation entitled **"TO STUDY THE EFFICACY OF ORMILOXIFENE IN THE MEDICAL MANAGEMENT OF AUB"**was done by me at The Institute Of Social Obstetrics, Govt Kasturba Gandhi Hospital & Institute of Obstetrics and gynaecology, Madras Medical College during 2014-2017 under the guidance and supervision of, **Prof. Dr. S. VIJAYA MD. DGO.** This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.S. Degree in Obstetrics and Gynaecology.

Place: Chennai
Date:

Signature of Candidate

DR. KANIMOZHI A
MS OG, Post Graduate Student
Madras medical college.
Chennai-5

Prof. DR. S. VIJAYA, M.D., DGO.
Professor/ , Director I/C.
Institute of Social Obstetrics
Madras medical college, Chennai-3

ACKNOWLEDGEMENT

I gratefully acknowledge and sincerely thank **Dr.M.K. Muralidharan, MS., MCH.,** Dean, Madras Medical College and Research Institute, Chennai for allowing me to use the facilities and clinical materials available in the hospital.

My sincere thanks and gratitude to **Dr.S.BabyVasumathi, M.D., D.G.O.,** Director and Superintendent, Institute of Obstetrics and Gynaecology, for granting me permission to utilize the facilities of the institute for my study.

I am extremely grateful to our Professor, **Prof. Dr. S.Vijaya, MD., DGO**. Professor / Director I/c, Institute of Social Obstetrics, Madras Medical College, for her valuable guidance, motivation, and encouragement given during the study.

My sincere thanks to the Professors and Assistant Professors of the Department of Obstetrics and Gynaecology for their help during this study.

I am immensely grateful to all the patients who took part in the study.

I thank my family for being the pillar of strength and unflagging support throughout.

ABBREVIATIONS

AUB	-	Abnormal Uterine Bleeding
DUB	-	Dysfunctional uterine bleeding
FSH	-	Follicular Stimulating Hormone
LH	-	Leutenising Hormone
TSH	-	Thyroid Stimulating Hormone
NAD	-	No Abnormalities Detected
USG	-	Ultrasonogram
AUB	-	Abnormal uterine bleeding
HMB	-	Heavy menstrual bleeding
HPMB	-	Heavy and prolonged menstrual bleeding
IMB	-	Intermenstrual bleeding
PMB	-	Postmenopausal bleeding
TIMP	-	Tissue Inhibitor Metallo Proteinases

CONTENTS

Introduction

INTRODUCTION

AUB is defined as bleeding from genital tract which is beyond the normal limits of quantity , timing and duration and is solely the diagnosis of exclusion.

Altered hypothalamic – pituitary- ovarian function or change in prostaglandin levels are the main cause for AUB. It causes heavy profuse bleeding . AUB is more common in anovulatory cycles than in ovulatory cycles.

Common drugs used for medical management of AUB includes non-steroidal anti-inflammatory drugs , antifibrinolytics , progesterone, estrogen progesterone combinations. Combined oral contraceptive pills , Danazol , GnRH analogues used in AUB has certain side effects so not preferred much . Medical management has always been the first therapeutic option and hysterectomy should be the last resort in the management of AUB. About 1/3 rd of hysterectomies are done for problems in menstruation. It results in unnecessary morbidities like premature menopause, bladder and bowel disturbances.

Ormeloxifene is a benzopyran Selective Estrogen Receptor Modulator (SERM), which blocks the cytosol receptors by its competitive binding over estradiol. It acts as antagonist in uterus and breast and agonist on vagina, bone, vascular endothelium and brain tissue. The effect of this SERM on the vascular endothelium leads to decrease in blood loss and thereby amelioration of symptoms in AUB.

Review of Literature

REVIEW OF LITERATURE

Any deviation from routine cyclical bleeding pattern is considered as abnormal uterine bleeding.

TERMS IN ABNORMAL UTERINE BLEEDING

Oligomenorrhoea	Cycle length lasting for >35 days
Polymenorrhoea	Cycle length lasting for <21 days
Menorrhagia	Normal cycle length (21 to 35 days) but with profuse bleeding (80 ml) or with increased duration (7 days)
Menometrorrhagia	Irregular unpredictable bleeding i.e associated with increased flow (80 ml) or duration (7 days)
Amenorrhoea	Absence of monthly cyclical bleeding for > 6 months in reproductive age group
Metrorrhagia or Intermenstrual bleeding	Intermittent bleeding between cycles
Midcycle spotting	Minimal bleeding that precedes ovulation
Postmenopausal bleeding	Any bleeding in postmenopausal women ie.after cessation of bleeding for >1yr
Acute emergent abnormal uterine bleeding	Excessive Bleeding that results in haemodynamic changes that manifests as increased heart rate / fall in BP
Dysfunctional uterine bleeding	Any abnormal uterine bleeding without any identifiable local or systemic causes

Menstrual cycles are defined in terms of

1. Regularity

2 .Frequency

3. Amount of blood loss

4. Period of bleeding

Any alteration in these terms results in AUB

1. Disturbances of Regularity:

***a . Irregular menstrual bleeding* :**

Any variation in the normal cyclical rhythm of bleeding is called irregular menstrual bleeding.

***b. Absent menstrual bleeding (amenorrhea*)**:

It is defined as cessation of menstrual cycle for 90 days.

2. Disturbances of Frequency

a. Infrequent menstrual bleeding :

It is defined as bleeding $\leq$ 2 episodes within 90 days.

b. Frequent menstrual bleeding*:*

It is defined as >4 episodes of regular menstrual bleeding within 90days.

3. Disturbances of Heaviness of Flow

a. Heavy menstrual bleeding :

HMB is blood loss which affects the quality of life of a reproductive age women. So all necessary steps should be taken to improve the quality of life. Pelvic congestion syndromes are associated with HMB.

b. Heavy and prolonged menstrual bleeding (HPMB):

It is the bleeding which lasts for > 8 days , associated with heavy menstrual blood loss.

c. Light menstrual bleeding:

It is the bleeding which is not profuse in amount and rarely stains the sanitary pads.

4. Disturbances of the Duration of Flow

a. Prolonged menstrual bleeding:

It is the menstrual bleeding that lasts for > 8 days in regular intervals and commonly associated with heavy flow.

b. S***hortened menstrual bleeding***:

It is the light menstrual bleeding that lasts no longer than 2 days.Genital TB, intrauterine adhesions have been implicated as causes.

c. Irregular Non-menstrual Bleeding:

It is associated with the Inter-menstrual bleeding or post-coital spotting .

d. Inter-menstrual bleeding:

It is irregular bleeding occurring around ovulation period.

e. Acyclical bleeding:

It is the menstrual bleeding without any cyclical pattern. Advanced Carcinoma of cervix or Carcinoma endometrium may be associated with acyclical bleeding.

- **Bleeding Outside Reproductive Age**

a. Precocious menstruation

It is the menstruation which occurs in < 9 years of age is precocious menstruation. It is very uncommon.

b.Postmenopausal bleeding

It is the bleeding which occurs after 1 year of amenorrhoea .

TYPES OF AUB :

Acute AUB :

It is the blood loss amounting to an extent which necessitates immediate intervention to prevent further loss.

Chronic AUB:

Any abnormal uterine bleeding which lasts for >6 months is called chronic AUB.

Bleeding Patterns in Women Using Hormonal Contraceptive

Bleeding	Any bleeding from genitals which needs sanitary pads or tampons.
Spotting	Any bleeding from genitals which is very minimal in quantity which does not necessitate sanitary pads
Bleeding/spotting episode	Bleeding which lasts for 1-2 days.
Bleeding/ spotting free interval	Bleeding or spotting free period for more than 1 day
Bleeding/spotting segment	Bleeding episode followed by bleeding free interval
Reference period	90 days is considered as reference period for women on long-acting hormonal treatment and 28 or 30 days for women on once a month pill

New Revised recommendations - bleeding patterns

No bleeding	No bleeding / spotting during reference period
Prolonged bleeding	≥ 10 days of bleeding / episode
Frequent bleeding	>4 episodes of bleeding / 90 days
Infrequent bleeding	< 2 episodes of bleeding / 90 days
Irregular bleeding	Varying bleeding free intervals lasting for > 17 days to 90 days

Characteristics of menstruation:

1. FREQUENCY :

Bleeding which occurs for every 24-38 days is said to be normal. If the cycle length is <24 days it is said to be frequent cycle, and if cycle length is >38 days , it is said to be infrequent cycle.

2. AMOUNT OF BLOOD LOSS :

Normally women loses about 5-80 ml of blood during menstruation. If the blood loss is >80 ml it is said to be heavy flow , and if the blood loss is <5ml it is said to be scanty flow**.**

3. DURATION OF FLOW :

Normal cyclical bleeding lasts for 4.5 to 8 days. If the cycle last for >8days it is said to be prolonged cycle and if it lasts for < 4.5 days it is said to be short cycle.

FIGO CLASSIFICATION – AUB :

AUB has replaced the term DUB. FIGO has standardised the nomenclature for AUB. PALM-COEIN is the acronym used for AUB categorization

Causes :

PALM - Polyp, Adenomyosis, Leiomyoma, Malignancy (and hyperplasia)

COEIN - Coagulatory disorders, Ovulatory disorders, Endometrial causes, Iatrogenic and Not otherwise classified .

Leiomyoma are classified depending on the sites into submucosal (SM) and other sites (O).

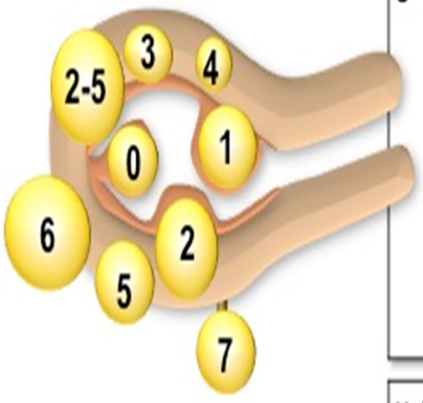
According to Wamsteker classification , further subdivided into 9 categories.

Polyp	
Adenomyosis	
Leiomyoma	
Malignancy & hyperplasia	

Submucous
Other

Coagulopathy
Ovulatory dysfunction
Endometrial
Iatrogenic
Not otherwise classified

Leiomyoma subclassification system



SM - Submucous	0	Pedunculated intracavitary
	1	<50% intramural
	2	≥50% intramural
O - Other	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserous ≥50% intramural
	6	Subserous <50% intramural
	7	Subserous pedunculated
	8	Other (specify e.g. cervical, parasitic)

Hybrid leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
	2-5	Submucous and subserous, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.

.

POLYPS (AUB-P)

These are endometrial stromal and glandular proliferations. It is best visualised by ultrasound , SIS , hysteroscopy.

ADENOMYOSIS (AUB-A)

It is the condition in which endometrial islands are found in the myometrium.

It is associated with leiomyomas , pelvic endometriosis , endometrial carcinomas.

USG findings of adenomyosis :

1. Ill-defined hypoechoic areas / heterogenous echoes in myometrial layer.
2. Asymmetrical uterine enlargement.
3. Sub-endometrial halo .
4. Endometrial infiltration of myometrium

AUB-LEIOMYOMA (AUB-L)

AUB associated with fibroids are due to varying causes:

1. Surface area of uterine endometrium is increased thereby increasing the amount of endometrium to be shedded off.
2. Fragile vessels around the leiomyoma can lead to increased flow
3. Complex molecular changes associated with fibroids leads to alteration in vasoactive substrates

4. Matrix metalloproteinase 2 and 11 levels are increased in fibroids increasing the release of lytic enzymes.
5. Increased expression of VEGF, basic fibroblast growth factor , heparin-binding EGF, platelet- derived growth factor (PDGF) leading to angiogenesis.
6. Alteration of plasminogen modulators
7. Altered IL-13, IL-17 and IL-10 inflammation leading to endometrial damage .

MALIGNANCY (AUB-M)

Malignancy can also present as AUB. Causes can be

1. Endometrial cancer
2. Cervical cancer
3. Uterine sarcoma
4. Long term use of tamoxifen
5. Previous pelvic radiation therapy
6. Hereditary leiomyomatosis
7. Renal cell carcinoma (HLRCC).

COAGULOPATHY (AUB-C) :

Coagulation disorders can present as AUB as well. Causes includes ,

1. Von Willebrand disease
2. Acquired ITP
3. Drug induced – heparin , coumarin.

Koudies scheme for coagulopathy :

Criteria

1.profuse bleeding since menarche

2. One of the following:

Postpartum haemorrhage

Bleeding after surgery.

Bleeding after dental procedures.

3. $\geq$ 2 of the following:

Easy Bruising 1-2 episodes /month

Nasal bleeds 1-2 episodes /month

Frequent bleeding from gums

hereditary bleeding disorders

OVULATORY (AUB-O)

It is due to the unopposed action of oestrogen on endometrium leading to endometrial hyperplasia.

Causes :

1. Polycystic ovarian syndrome
2. Hyperprolactinaemia
3. Hypothyroidism
4. Obesity
5. Anorexia.

ENDOMETRIAL (AUB-E)

Endometrial causes are due to the abnormal secretion of prostaglandins leading to abnormal haemostasis .

Causes :

1. TB endometritis
2. Chlamydial infection

IATROGENIC (AUB-I) :

Any drug supplementation which leads to unregulated endometrial bleeding is said to be iatrogenic AUB.

Causes :

1. Oestrogen or progestin
2. GnRH agonists

3. Aromatase inhibitors
4. Selective Oestrogen Receptor Modulators (SERM)
5. Selective Progesterone Receptor Modulators (SPRM)

NOT OTHERWISE CLASSIFIED (AUB-N)

Cause of AUB which does not fit into any categories of PALM-COEI.

Causes :

1. AV malformations of uterus
2. Pseudoaneurysms of endometrium
3. Myometrial hypertrophy
4. Chronic endometritis.

EVALUATION OF ABNORMAL UTERINE BLEEDING

DIAGNOSTIC STEPS	PERTINENT SIGNS, SYMPTOM , TESTS	CONDITIONS
HISTORY	Pelvic pain	Miscarriage , ectopic , PID , trauma , sexual abuse or assault
	Nausea, weight gain , urinary frequency, fatigue	pregnancy
	Weight gain , cold intolerance , constipation , fatigue	hypothyroidism
	Weight loss , sweating , palpitations	hyperthyroidism
	Easy bruising , tendency to bleed	coagulopathy
	Jaundice , hepatitis history	Liver disease
	Hirsuitism , acne, acanthosis nigricans, obesity	PCOS
	Post-coital bleeding	Cervical dysplasia , endo-cervical polyps

	Galactorrhoea , headache, visual-field disturbances	Pituitary adenoma
	Weight loss , excessive exercise, stress	Hypothalamic suppression
PHYSICAL EXAMINATION	Thyromegaly , weight gain , edema	hypothyroidism
	Thyroid tenderness , tachycardia , weight loss , velvety skin	hyperthyroidism
	Bruising , jaundice , hepatomegaly	Liver disease
	Enlarged uterus	Pregnancy, leiomyoma , uterine cancer
	Firm , fixed uterus	Uterine cancer
	Adnexal mass	Ovarian tumour , ectopic , cyst
	Uterine tenderness, cervical motion tenderness	PID , endometritis

LABORATORY TESTS	Beta-HCG	pregnancy
	CBC , platelet counts , coagulation profile	coagulopathy
	Liver function tests , Prothrombin time	Liver disease
	Thyroid stimulating hormone	Hypothyroidism , hyperthyroidism
	prolactin	Pituitary adenoma
	Blood glucose	Diabetes mellitus
	DHEAS, free testosterone ,17 OH progesterone	Ovarian or adrenal tumour
	Papanicolau smear	Cervical dysplasia
	Cervical testing for infection	Cervicitis , PID

IMAGING AND TISSUE SAMPLYING	Endometrial biopsy or dilatation & curettage	Hyperplasia , atypia , adenocarcinoma
	Transvaginal ultrasonography	Pregnancy , ovarian or uterine tumours
	Saline infusion sono hysterography	Intracavitary lesions , polyps , sub-mucous fibroids
	hysteroscopy	Intracavitary lesions ,polyps , sub-mucous fibroids

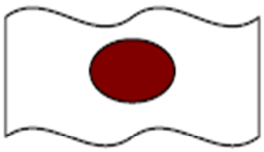
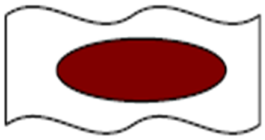
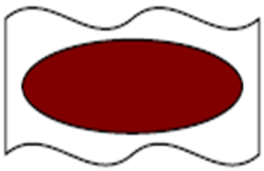
MENSTRUAL BLOOD LOSS – MEASUREMENTS :

1. THE ALKALINE HEMATIN TEST

It is by extracting hemoglobin from the sanitary pads and converting to hematin and measured by spectrophotometry.

It is rarely used and not preferred over other techniques.

2. Pictorial Blood Loss Assessment Charts (PBAC)

Score	Number of pads per day	Number of days							
		1	2	3	4	5	6	7	8
1		☐	☐	☐	☐	☐	☐	☐	☐
5		☐	☐	☐	☐	☐	☐	☐	☐
20		☐	☐	☐	☐	☐	☐	☐	☐
1	Small blood clots	☐	☐	☐	☐	☐	☐	☐	☐
5	Big Blood Clots	☐	☐	☐	☐	☐	☐	☐	☐

Higham has devised a scoring system for assessing the amount of menstrual blood loss. PBAC Score · 100 is equivalent to >80 ml of menstrual blood loss , which is considered as heavy menstrual bleeding . It is one of the accurate methods to assess the exact blood loss.

3. Self-assessment measures

Self assessment symptoms includes

1. An unusual profuse bleeding
2. >7 days of bleeding
3. Flooding of pads
4. Associated passage of clots >3 cm.

PATHOGENESIS OF ABNORMAL UTERINE BLEEDING:

MECHANISM OF NORMAL MENSTRUATION

WITHDRAWAL OF ESTROGEN / PROGESTERONE

↓

INSTABILITY OF LYSOSOMAL MEMBRANE

↓

RELEASE OF LYTIC ENZYMES

↓ ↓

VASCULAR ENDOTHELIUM	RELEASE OF INFLAMMATORY MEDIATORS
Platelet aggregation	Increased inflammatory markers (COX2,CXCL2,IL8)
Prostaglandin release	Increased metalloproteinase levels
Thrombosis	Breakdown of basal arterioles
Tissue necrosis	

↓

MENSTRUATION

MECHANISM OF CESSATION OF MENSTRUATION

FSH mediated E2 release

↓

REGENERATION OF ENDOMETRIUM

↓

VEGF MEDIATED ANGIOGENESIS

↓

PLATELET PLUG FORMATION

↓

CESSATION OF MENSTRUATION

MECHANISM OF DYSFUNCTIONAL UTERINE BLEEDING

Types of DUB :

1. **Ovulatory DUB** :
    a. Metropathia haemorrhagica
    b. Threshold bleeding
2 . **Anovulatory DUB**
    a. luteal phase defect
    b. idiopathic menorrhagia

Mechanism of ovulatory DUB.

1. Altered ratio of vasodilatory and vasoconstrictory prostaglandins
2. Increased prostaglandin level
3. Poor aggregation of platelets
4. Increased proteolytic lysosomal enzyme
5. Fall in estrogen levels prior to ovulation
6. Progesterone withdrawal leading to bleeding

Anovulatory dysfunctional bleeding

Physiological :

1. Adolescence
2. Perimenopause
3. Lactation
4. Pregnancy

Pathologic :

1. Thyroid disease
2. Premature ovarian failure
3. Chemo drugs
4. Medications
5. Hyperandrogenic anovulation (e.g., PCOS, CAH, or androgen-producing tumors)
6. Hypothalamic dysfunction
7. Hyper prolactinemia
8. Pituitary

TREATMENT OF DYSFUNCTIONAL UTERINE BLEEDING

A.Conservative management:

I. Non-hormonal drugs

a. NSAID

b. Tranexamic acid

c. Ethamsylate

II. Hormonal treatment

a. Progestogens

b. oc pills

c. Danazol

d. GnRH analogues

III. Levonorgestrel-releasing intrauterine system

lV. SERM - ormiloxifene

B. Minimally invasive surgery :

Abalative technique

a. 1 st generation

b. 2^{nd} generation

C. Surgical management

I. Hysterectomy

A.CONSERVATIVE MANAGEMENT :

Correction of anaemia with haematinics should be the step in management of AUB.

It is the first line of management in any reproductive age women with AUB.

1. Non-hormonal medications :

a. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

The mechanism is by inhibiting prostaglandin synthesis.

Drugs used are,

1. Mefenamic acid
2. Naproxen
3. Ibuprofen
4. Flurbiprofen
5. Meclofenamic acid
6. Diclofenac,
7. Indomethacin
8. Acetylsalicyclic acid

Advantanges:

1. Used only during menses
2. Low side effects
3. Relieves dysmenorrhea

Side effects :

- headache
- GI symptoms
- dyspepsia.

Contraindications :

- gastrointestinal ulcers
- asthma
- allergy

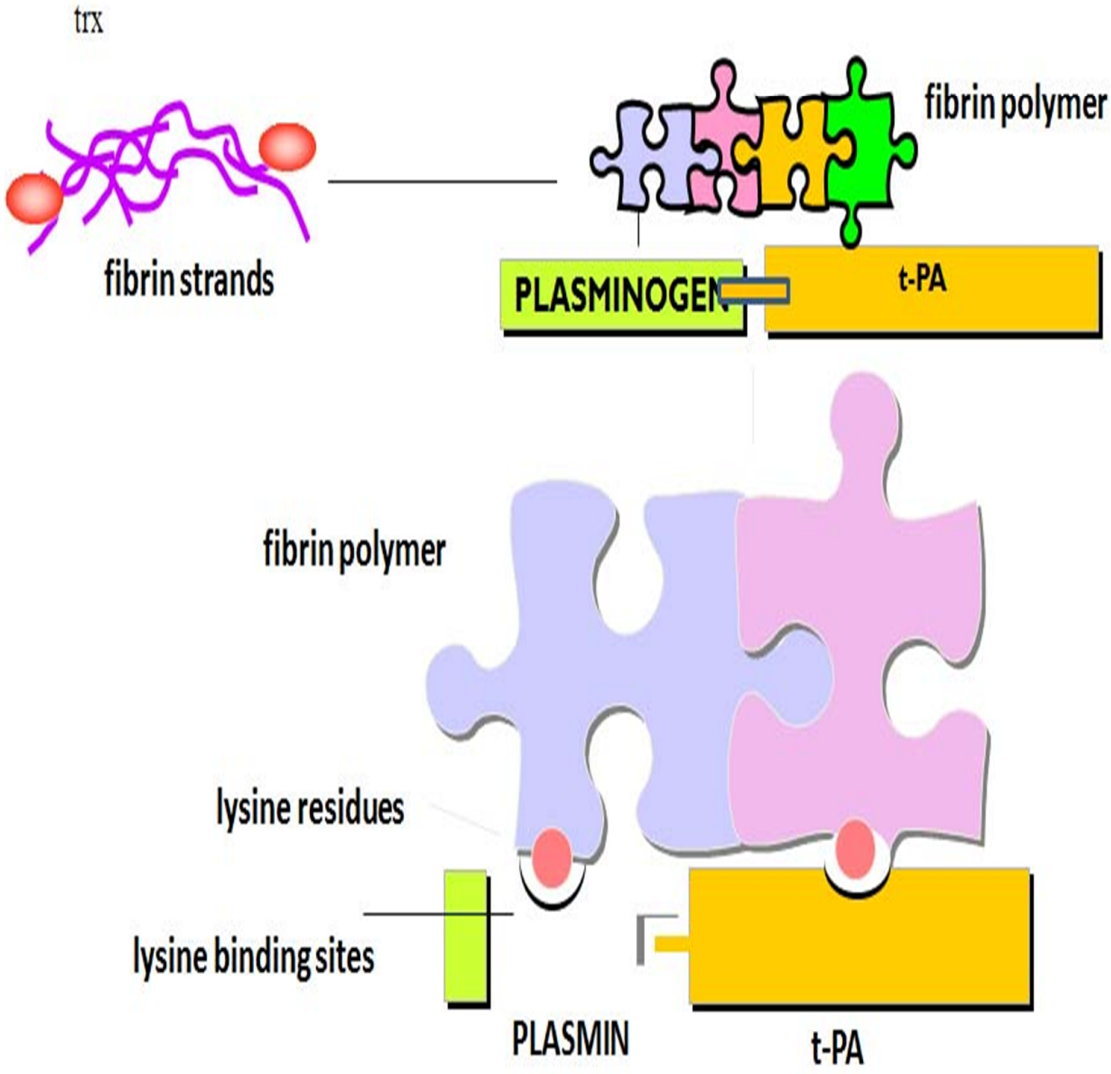
b.Tranexamic acid

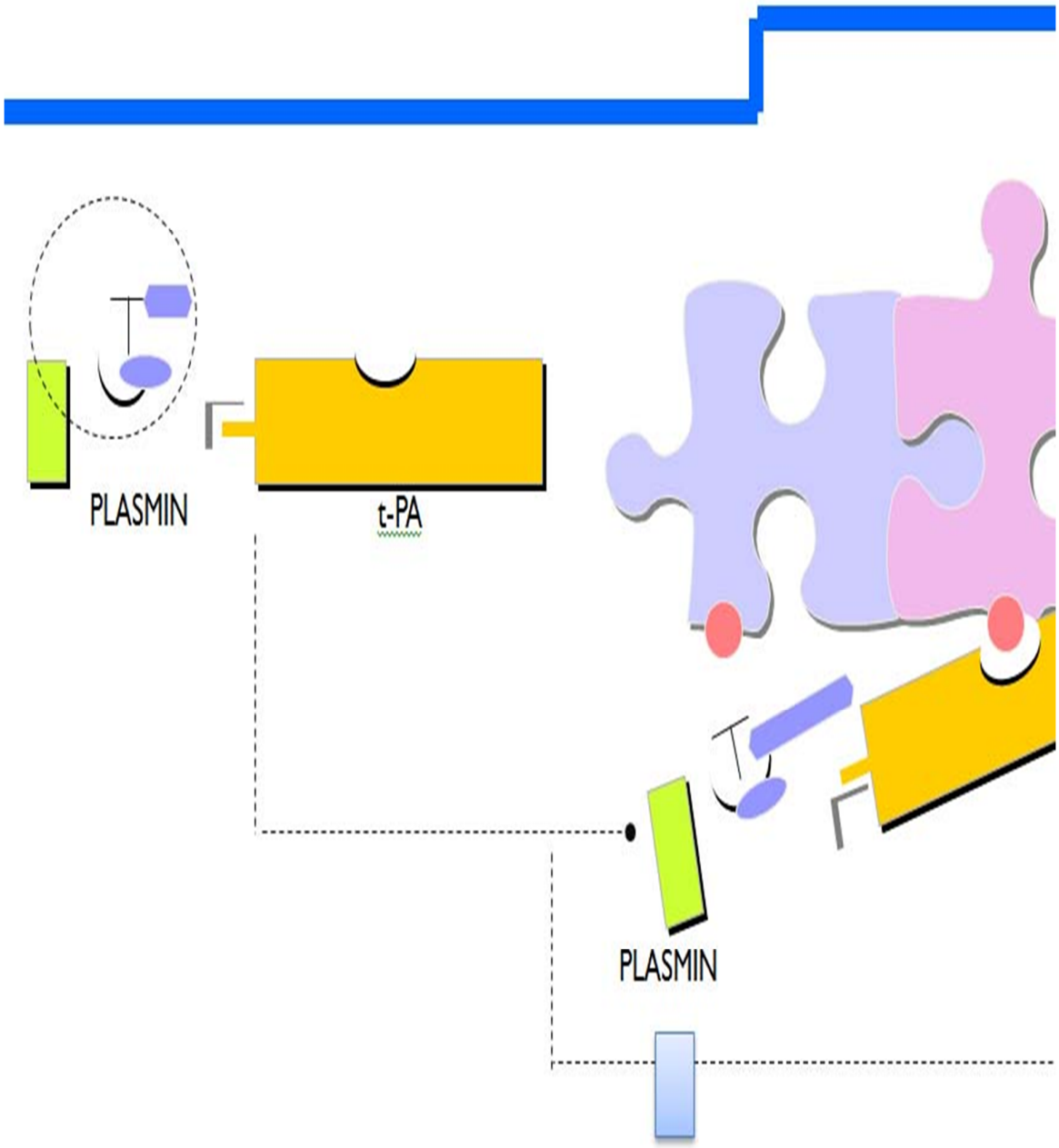
It is a synthetic lysine amino acid derivative.

Mechanism of action :

a. By exerting anti-fibrinolytic activity since endometrium is rich in plasminogen activators in case of AUB
b. There is reversible blockade of lysine binding sites on plasminogen molecules, thus inhibiting the activation of plasminogen to plasmin or fibrinolysin.
c. It stabilizes the fibrin structure and prevents untimely dissolution of the clot

MECHANISM OF ACTION:




PLASMIN
t-PA
PLASMIN

DOSAGE : 1 g every 6 th hrly daily until heavy flow lasts .

ADVANTAGE :

Bleeding reduces by 50%

SIDE EFFECTS :

- May be linked with thrombogenic disease.
- Headache
- Musculoskeletal pain
- Sinus & nasal symptoms
- Fatigue

c. Ethamsylate

It is epsilon amino caproic acid.

It reduces capillary fragility.

It can be used along with tranexamic acid.

3. HORMONAL MEDICATIONS :

a. Progesterones :

Mechanism includes

- Can act only on estrogen primed endometrium(not on thin eroded endometrium).
- Inhibit estrogen receptor replenishment
- Induces conversion of estradiol to less active estrone
- Synthetic Progesterones have ANTIMITOTIC EFFECT leading to atrophy of endometrium

- Uniform decidualisation &synchronous shedding

Oral progestins

↓	↓
Ovulatory	Anovulatory
Norethisterone	
5mg bd/tds (D16-25)	5mg tds (D5-D26)
MPA	
10mg OD (D16-D25)	10mg tds (D5-D26)

For profuse bleeding

A. Norethisterone 15 mg /day
B. Medroxyprogesterone acetate 30 mg / day till bleeding ceases maintenance dose for 3-4 weeks free of bleeding
C. Gestrinone orally 2.5 mg twice weekly / 5mg vaginal tablet 3 times/week for 6 months.
D. DMPA injections – reduces the number of cycles / year

Side effects :

Fatigability, mood swings, bloating, pedal edema, headache, depression, loss of libido, intermenstrual bleeding and atherogenic lipid profile

b. Oral contraceptives

Mechanism includes

It inhibits ovulation and causes cyclical denudation of endometrium.

For severe acute bleeding

one pill 6^{th} hrly / day * 4 days

8^{th} hrly/ day * three days

12^{th} hrly/day * daily for two days

One pill/ day *21 days.

Contraindications of oral contraceptives :

1. History of stroke / DVT
2. History of any breast cancer / endometrial cancer
3. Liver disorders
4. Pregnancy,
5. Dyslipidemia
6. >15 cigarettes usage / day in perimenopausal women

c. ESTROGEN :

They are very effective in acute profuse bleeding.

Mechanism includes

1. By producing vasospasm
2. By affecting level of factor iv ,x fibrin
3. By improving platelet aggregation ,capillary permeability
4. Inducing progesterone receptor formation

   Endometrial and breast cancer risk are increased if estrogen alone therapy is instituted.

d. Danazol

It is a testosterone derivative

Main mode of action is by hindering the ovulation leading to endometrial atrophy.

Recommended dose 100- 200 mg/day for 3-4 cycles

Side effects :

1. Pimples
2. Excessive secretion of sebum leading to seborrhoea
3. Male pattern hair distribution
4. Virilisation
5. Gain of weight
6. Mood swings
7. Joint pain
8. Atrophy of breast tissue
9. Liver adenomas

e. GnRH analogues:

a. Depot injections (3.6 mg given monthly for 4-6 months)

b. GnRH Implant

Used prior to hysteroscopy can reduce operating time.

Side effects :

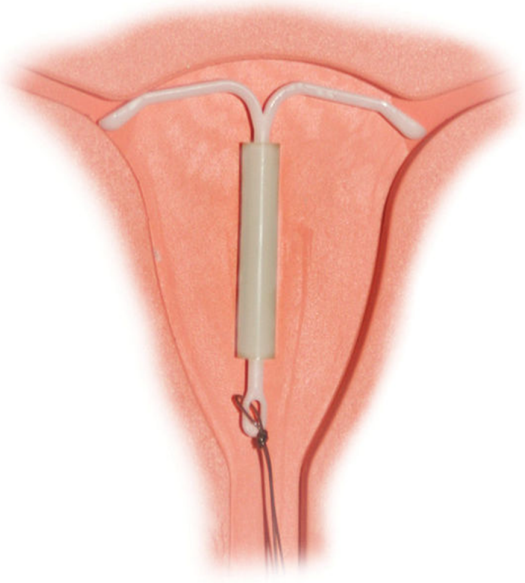
- Menopausal symptoms
- Osteoporosis
- Takes longer than 1 month to act.

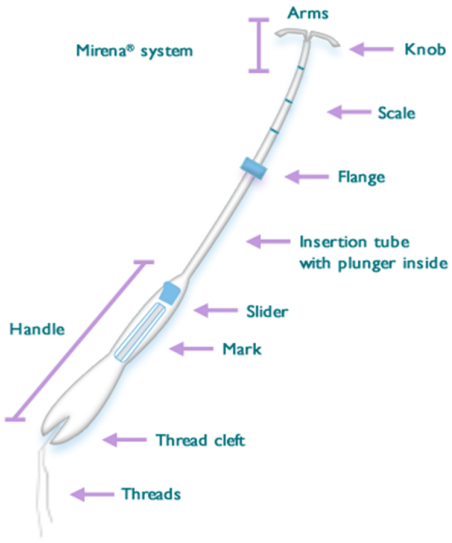
III. Levonorgesterol-releasing intrauterine system

Levonorgestrel-releasing intrauterine system was first developed as a contraceptive device which does not suppress ovulation.

1. It is T-shaped IUD with levonorgesterol of which 20 µg/ daily is released.

2. Preventing the thickening of endometrium thereby reducing the blood loss upto 90%





Side effects :

1. Bloating
2. Mastalgia
3. Irregular menstruation..

Advantages :

1. Relieves dysmenorrhea
2. Reduced PID due to the increased viscocity of utero-cervical mucus
3. Can be used in women of any reproductive age

Disadvantages :

1. Technical difficulty in insertion
2. Risk of ectopic pregnancy 0.2/100 women
3. Takes longer duration for effective action
4. Chances of amenorhoea upto 20 %

The technical difficulties of MIRENA insertion can be overcome by new devices like EMILY which enable easy insertion and better patient acceptability.

IV.Hysterectomy

Surgical removal of the offending organ has been considered the cornerstone of management of menstrual irregularities. In modern era hysterectomy alone is not the only weapon available in our treatment arsenal**.**

Hysterectomy is the definitive surgical treatment for menorrhagia and menstrual disorders.

Various available routes of hysterectomy include

1. Laparoscopic approach
2. Vaginal hysterectomy
3. Abdominal hysterectomy

Indications :

Failed medical management.

Not desirous for pregnancy.

Complications:

- Intraoperative complications-hemorrhage,damage to adjacent organs.
- Premature menopause
- Vault prolapse
- Dyspareunia
- Bowel and bladder disturbances
- Psycological problems.

B. MINIMALLY INVASIVE SURGERY :

Endometrial abalative techniques:

Mechanism of action:

It destroys about 2-3 mm of myometrium.

1. First generation techniques:

- Hysteroscopic endometrial ablation by resectoscope
- Loop
- Rollerball coagulation
- laser coagulation

2. Second generation techniques:

- Radiofrequency induced thermal ablation
- Cavaterm ballon therapy
- Microwave endometrial abaltaion
- Laser therapy

3. Uterine tamponade

4. Bilateral uterine artery embolization

1.Hysteroscopic Endometrial Abalation:

It is done postmenstrually.

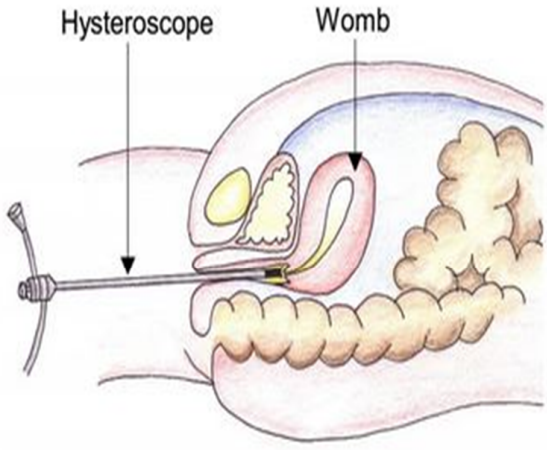


Figure 1

Hysteroscopic endometrial ablation

Contraindication

- Genital infections
- Uterine or preinvasive cancers
- Myomectomy or previous surgeries
- Desire for pregnancy
- Leiomyomas

2.Transcervical Resection Of Endometrium :

In this technique 4-5 mm of myometrium is destroyed. In VERSAPOINT – bipolar electrodes are used for resection.

Complications :

1. Due to anesthesia
2. Fluid imbalance leadig to pulmonary edema , hyponatremia , hypertension , shock
3. Injury to adjacent structures
4. Cervical stenosis leading to haematometra
5. Recurrence rate of 25 %

3. Radiofrequency Induced Thermal Ablation :

In this technique 0.6 mm metallic probe is inserted through cervix which releases the Electromagnetic thermal energy which destroys endometrium at 66 degree Celsius andprobe is rotated at 360 degree angle for 20 min.

Advantages :

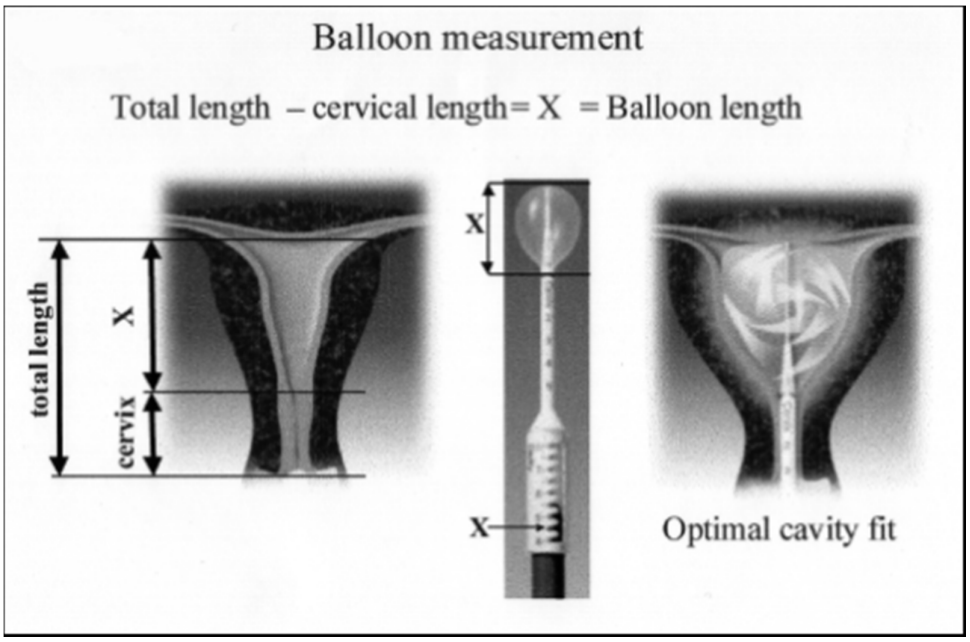
Less skill required

4. Cavarterm Ballon Therapy :

A silicon ballon is inserted into uterine cavity and distended with media.

87 degree celsius is maintained for 8 min over pressure of 160-180Hg as tamponade.

In this procedure about 6mm of endometrium is destroyed.



5. Microwave Endometrial Abalation:

This technique uses magnetic field to produce ablation upto 6 mm. About 80 degree celsius is maintained for 3 min duration to produce abalation.

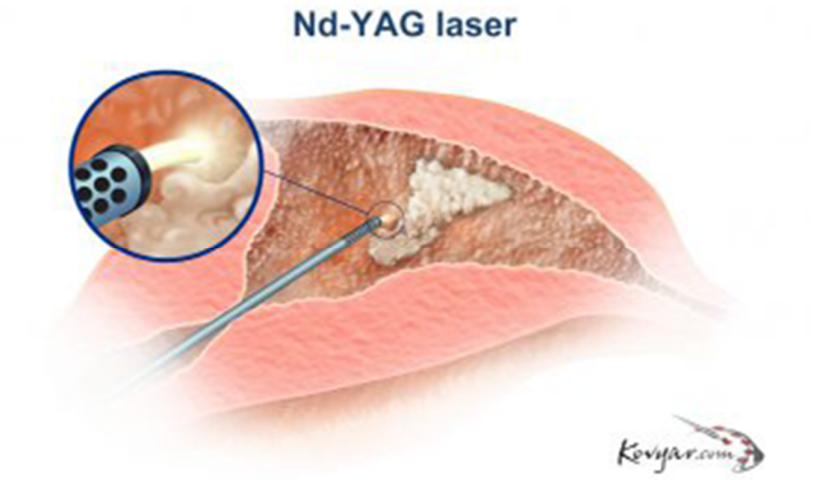
6. Novasure :

Uses bipolar radiofrequency to vaporize the uterine lining upto myometrial layer. It takes about 1.5 minutes to abalate the endometrium.

7. Endometrial Laser Intrauterine Thermotherapy : ELITT / GYNAELASE

Destroys the entire endometrium and upto 3mm of myometrium

Takes approximately 7 minutes for abalation.



3. Uterine Tamponade:

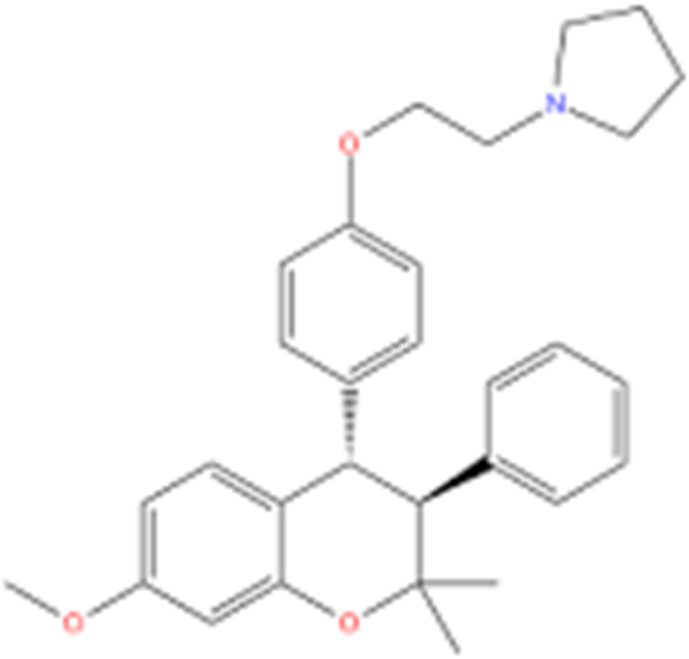
Foley catheter is inserted and distended with 30 ml fluid and left for 1 day

4. Bilateral Uterine Artery Ligation :

It is done in cases of intractable AUB / unfit for surgery /Av malformations.

IV. ORMILOXEFENE

Ormiloxifene / centchroman was first developed by central drug research institute,lucknow as a contraceptive pill . Its Indian trade name is saheli. Other brand names include sevista , novax.



INDICATIONS:

Contraception:

Dose :twice a week as 30mg tablet beginning on day one of cycle for twelve weeks the dose can be reduced to weekly once after 3 months.

Fertility returns within 6 months of stoppage of drug.

Post coital contraception:

wo pills given within 24 hrs of coitus followed by another dose 12 hours later. Other uses: Treatment of menstrual irregularity

Method of action:

Ormeloxifene is a SERM , or selective estrogen receptor modulator.

1. It is an estrogen agonist in bones while antagonist in uterus and ovary.
2. It doesn't cause ovulation inhibition.
3. It inhibits estrogen mediated priming and proliferation of endometrium.
4. It speeds the transport of the fertilized egg through the fallopian tubes more quickly than normal.
5. The fertilised egg arrives too soon into a non-conducive endometrium leading to

   failure of implantation .

Contraindications:

- Liver disease
- Renal disease
- PCOD
- Dysplastic cervix
- Drug allergy.

Pharmacokinetics:

Absorption:

By oral route absorbed easily via mesenteric vessels reaching the peak serum concentration within 240 minutes.

Distribution:

Not bound to plasma proteins.

Excretion:

Terminal half-life is approximately 170 hr.

Aims & objectives

AIMS AND OBJECTIVES

1. To study the efficacy of ormiloxifene in AUB.
2. To study the acceptability of drug among patients treated for AUB
3. To study the adverse effects of drug.
4. To study the failure rate and recurrence of AUB in patients treated with ormiloxifene.

Materials & methods

MATERIALS AND METHODS

Setting :

Institute Of Obstetrics, Egmore And Government Kasturba Gandhi Hospital , Triplicane.

Study population:

A prospective study was carried out in patients attending ISO & KGH and IOG at gynaec opd diagnosed as AUB after initial evaluation . Patients with AUB over the age of 35 years who have completed their family were enrolled in the study after obtaining written informed consent.

Data collection:

The demographic profile of patients enrolled for the study were noted .

Statistical analysis:

The repeated measures anova statistical tool was used to find the difference in three period. SPSS 20 version was used.

INCLUSION CRITERIA :

Patients presenting with abnormal uterine bleeding were recruited for study after detailed gynecological examinations and investigations to rule out any uterine pathology , congenital malformation and other organic causes for AUB.

EXCLUSION CRITERIA :

1. Leiomyoma
2. Endometriosis
3. Malignancies of genital tract
4. Liver dysfunction
5. Heart disease
6. Coagulopathies
7. Renal disease
8. Pregnancy
9. Iucd or pill users
10. Lactating women in the first 6 months of postnatal period
11. Thyroid disorder
12. History of abortion within last 3 months
13. Hypersensitivity to drug

Pretreatment evaluation:

Two pretreatment baseline menstrual cycles were compared with cycles after ormiloxifene treatment.

Parameters assessed are

a. Haemoglobin estimation.

b. Endometrial thickness in proliferative phase by transvaginal sonography..

c. Menstrual blood loss by pictorial blood loss assessment chart.

Scoring was assigned based on number, area of soakage and presence of clots. score of >150 was considered excessive.

Treatment protocol :

Patients enrolled for the study were given tablet ormiloxefene 60 mg initially two times a week for the initial 3 months following which dose was reduced to once per week for the remaining 3 months.

Post treatment outcome assessment :

Primary outcome:

a**.** Haemoglobin estimation.

b. Endometrial thickness in proliferative phase by transvaginal sonography.

c. Menstrual blood loss

Secondary outcome :

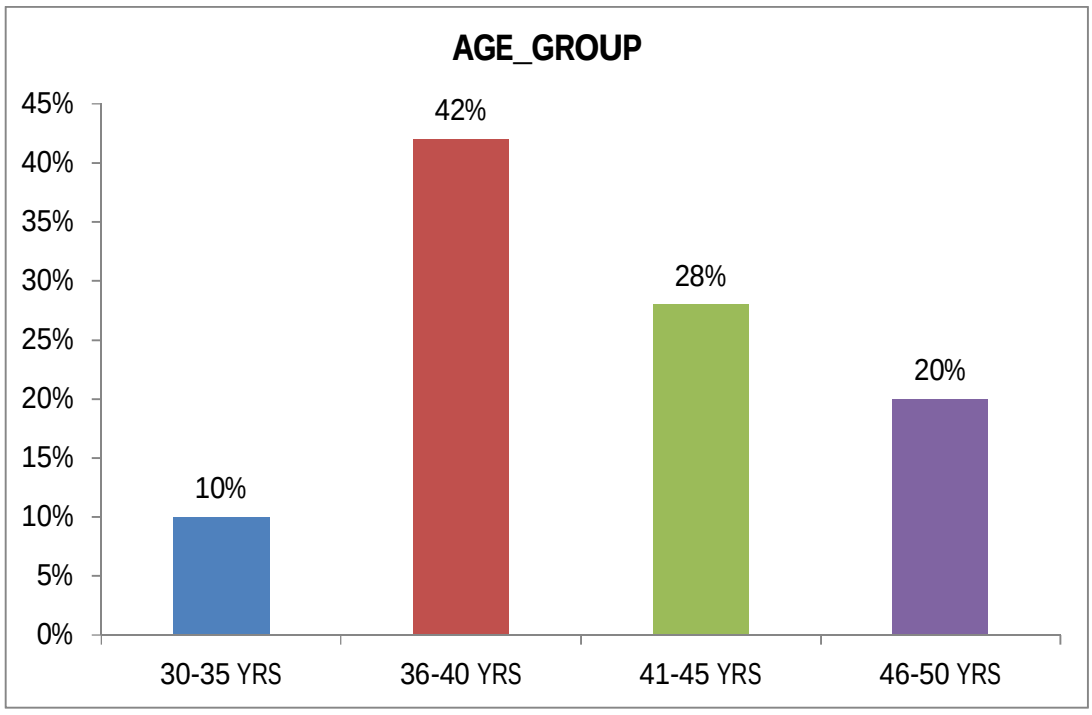
Acceptability of ormiloxifene in patients treated for AUB.

Observation & Analysis

RESULTS AND ANALYSIS

A. AGEWISE DISTRIBUTION OF CASES

		Frequency	Percent
Valid	30-35 YRS	10	10.0
	36-40 YRS	42	42.0
	41-45 YRS	28	28.0
	46-50 YRS	20	20.0
	Total	100	100.0

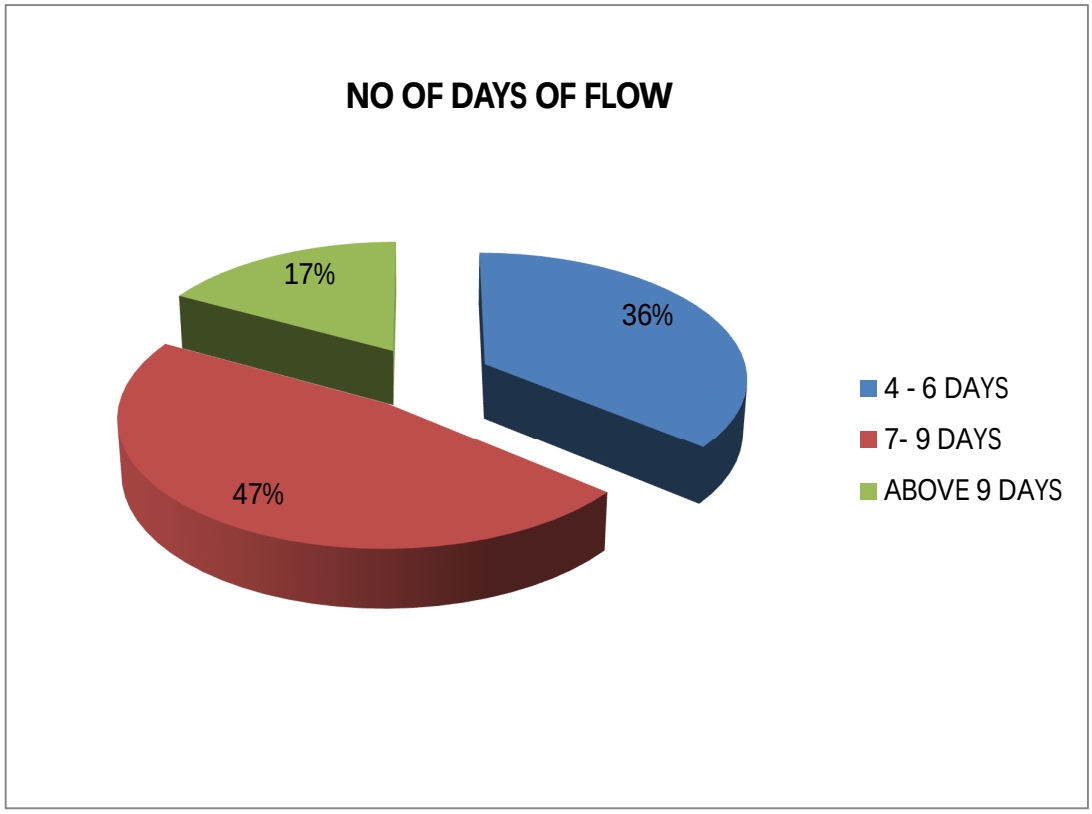


B.NO OF DAYS OF FLOW IN CASES UNDER STUDY

		Frequency	Percent
Valid	4 - 6 DAYS	36	36.0
	7- 9 DAYS	47	47.0
	ABOVE 9 DAYS	17	17.0
	Total	100	100.0

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
NO OF DAYS OF FLOW	100	4.00	13.00	7.5600	2.08079

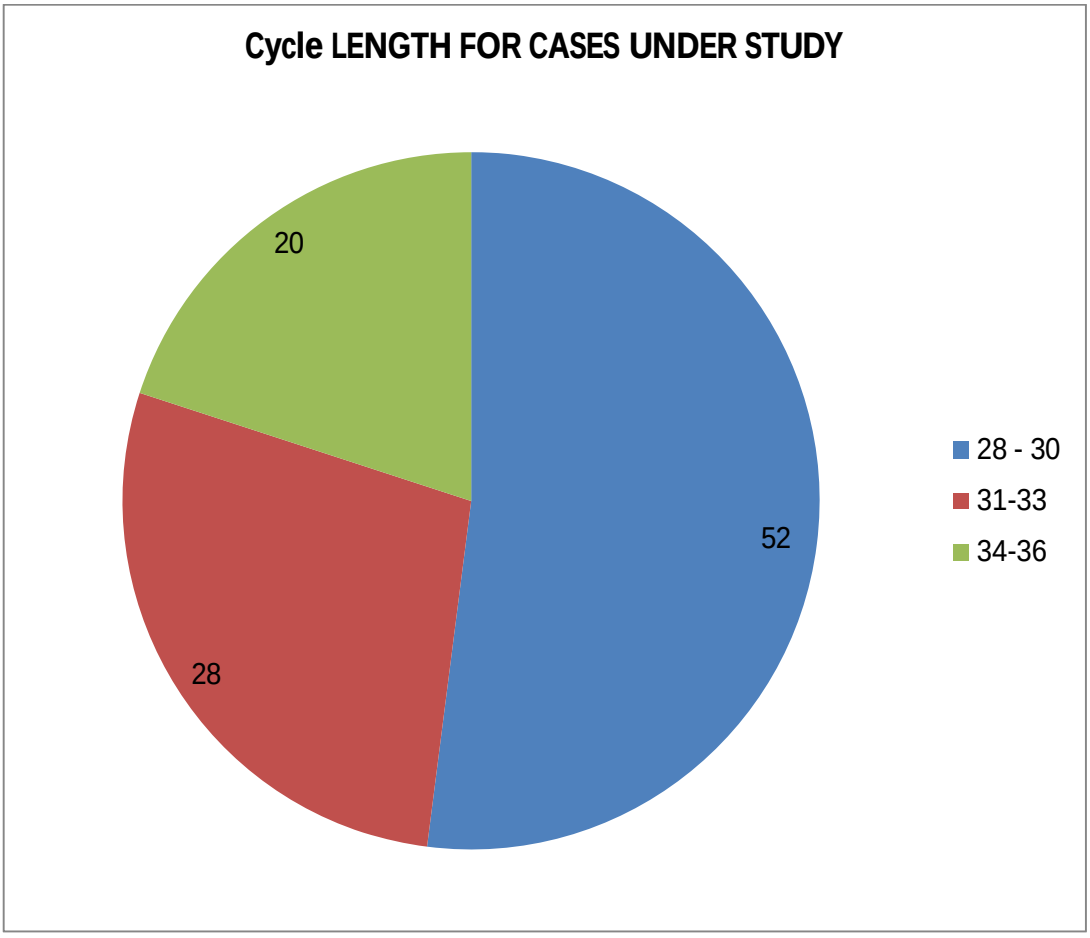

NO OF DAYS OF FLOW
17%
36%
47%
4 - 6 DAYS
7- 9 DAYS
ABOVE 9 DAYS

C.CYCLE LENGTH OF CASES UNDER STUDY

		Frequency	Percent
Valid	28 – 30	52	52.0
	31-33	28	28.0
	34-36	20	20.0
	Total	100	100.0

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
CYCLE LENGTH	100	28.00	36.00	31.0400	2.13636

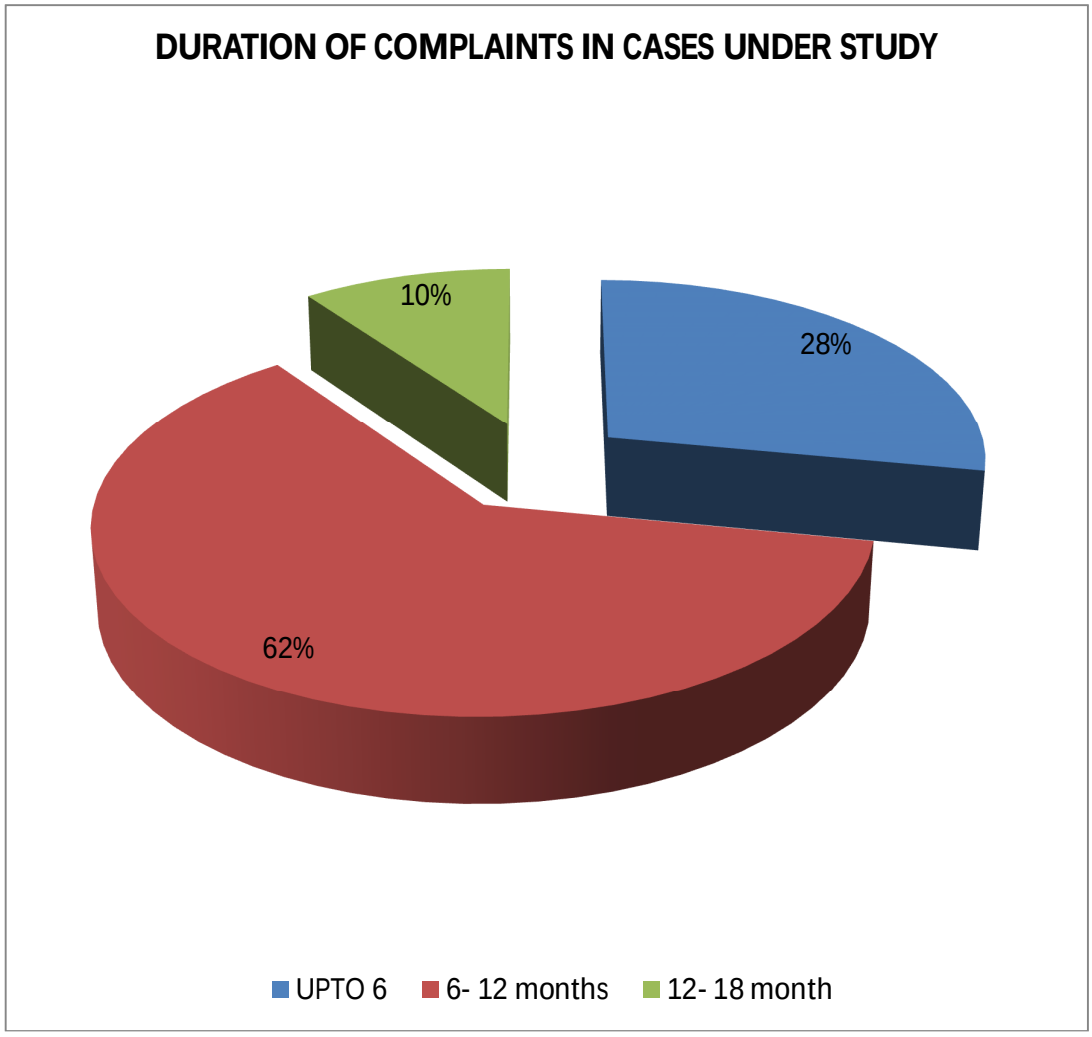

Cycle LENGTH FOR CASES UNDER STUDY
20
52
28
28 - 30
31-33
34-36

D.DURATION OF COMPLAINTS FOR CASES UNDER STUDY

		Frequency	Percent
Valid	UPTO 6	28	28.0
	6-12	62	62.0
	12-18	10	10.0
	Total	100	100.0

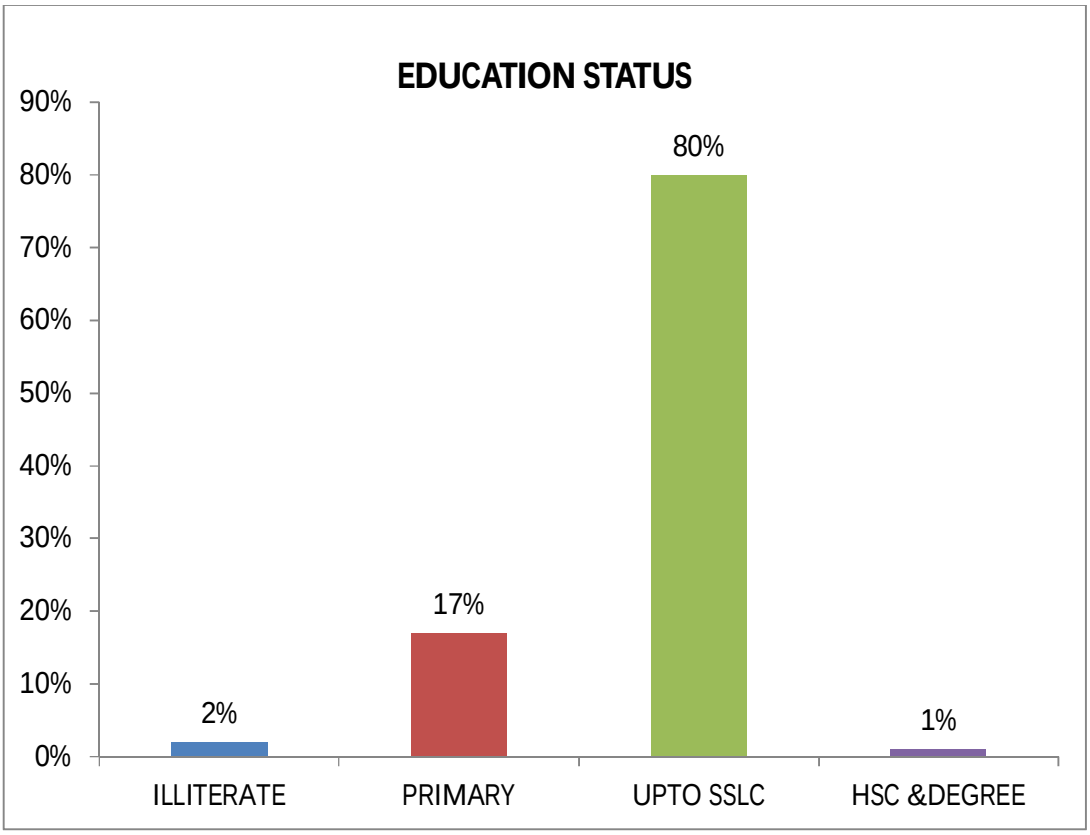
Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
DURATION OF COMPLAINT _MONTH_	100	5.00	18.00	8.9200	2.90134


DURATION OF COMPLAINTS IN CASES UNDER STUDY
10%
28%
62%
UPTO 6
6- 12 months
12- 18 month

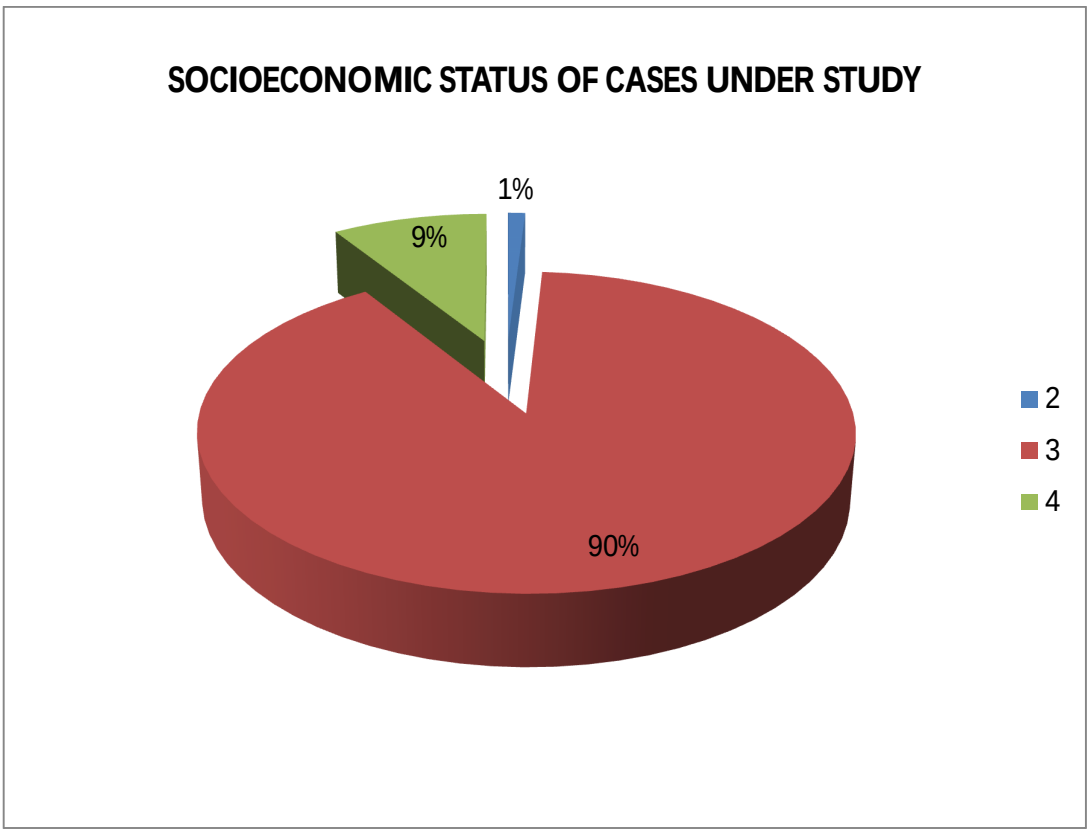
E.EDUCATION GROUP UNDER STUDY

		Frequency	Percent
Valid	ILLITERATE	2	2.0
	PRIMARY	17	17.0
	UPTO SSLC	80	80.0
	HSC &DEGREE	1	1.0
	Total	100	100.0



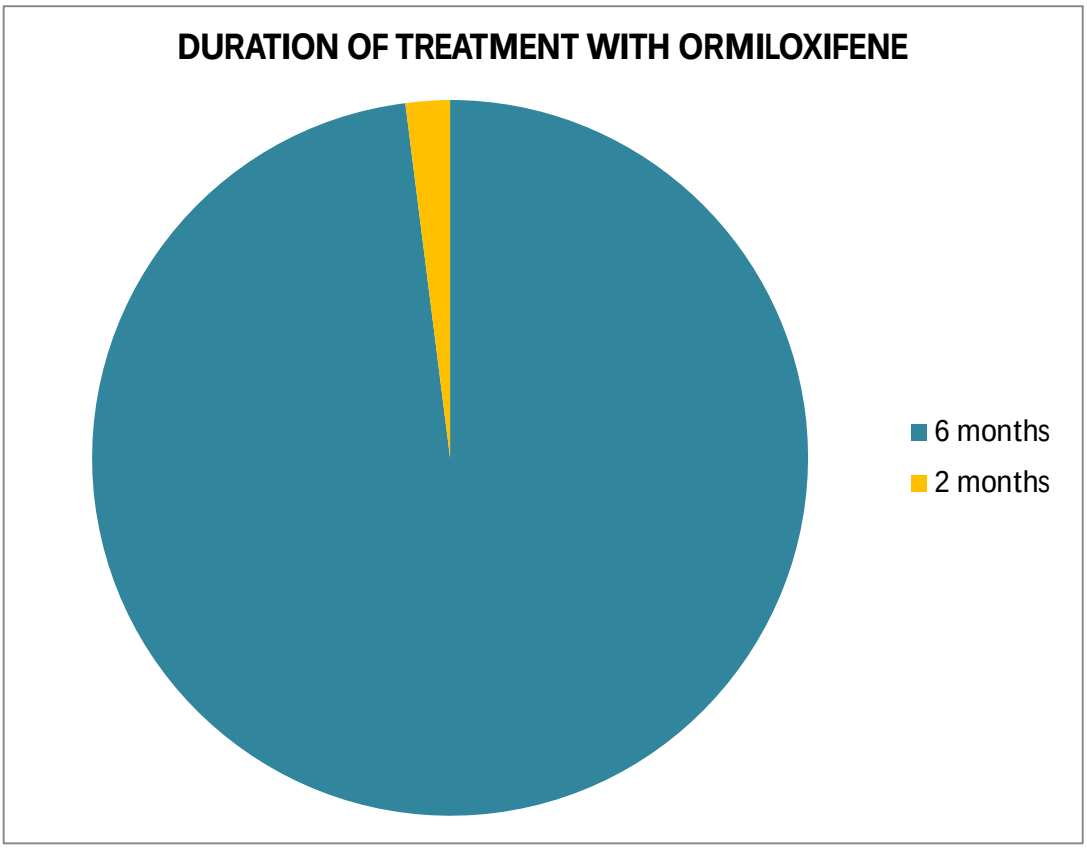
F.SOCIOECONOMIC STATUS OF CASES UNDER STUDY

		Frequency	Percent
Valid	2.00	1	1.0
	3.00	90	90.0
	4.00	9	9.0
	Total	100	100.0



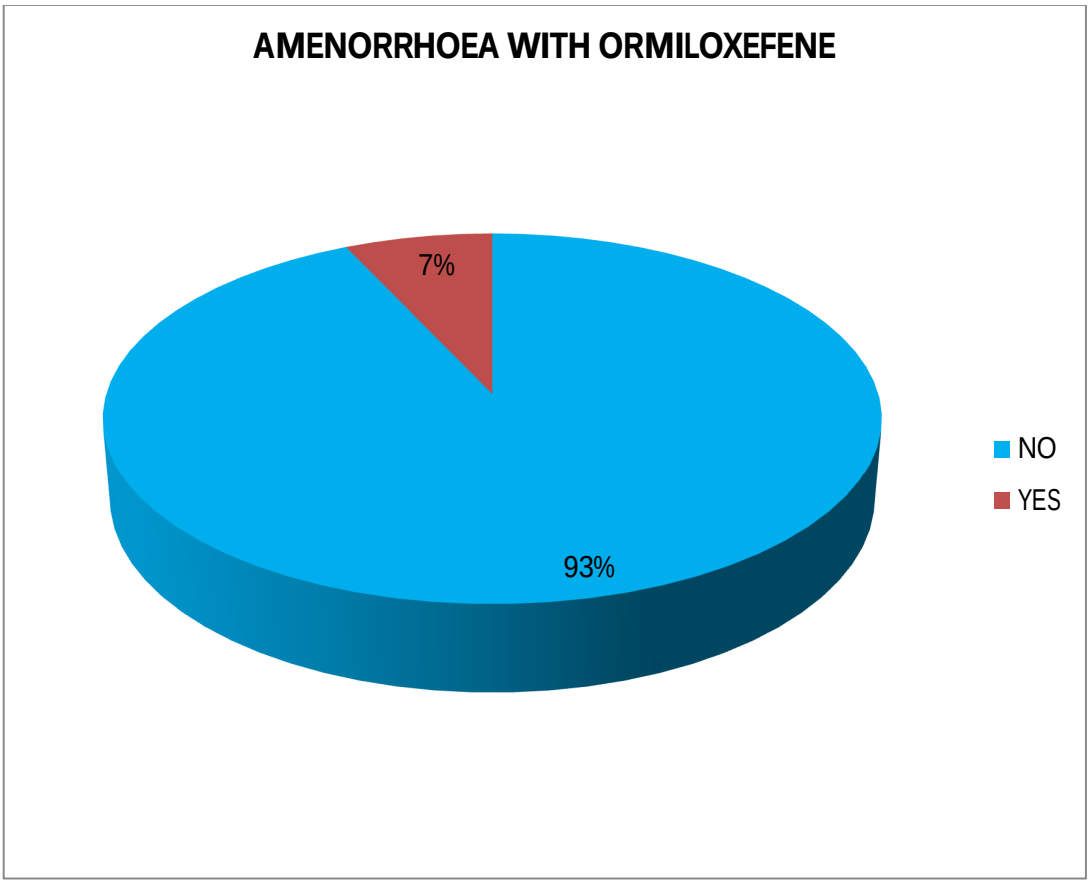
G.DURATION OF TREATMENT

		Frequency	Percent
Valid	3.00	2	2.0
	6.00	98	98.0
	Total	100	100.0



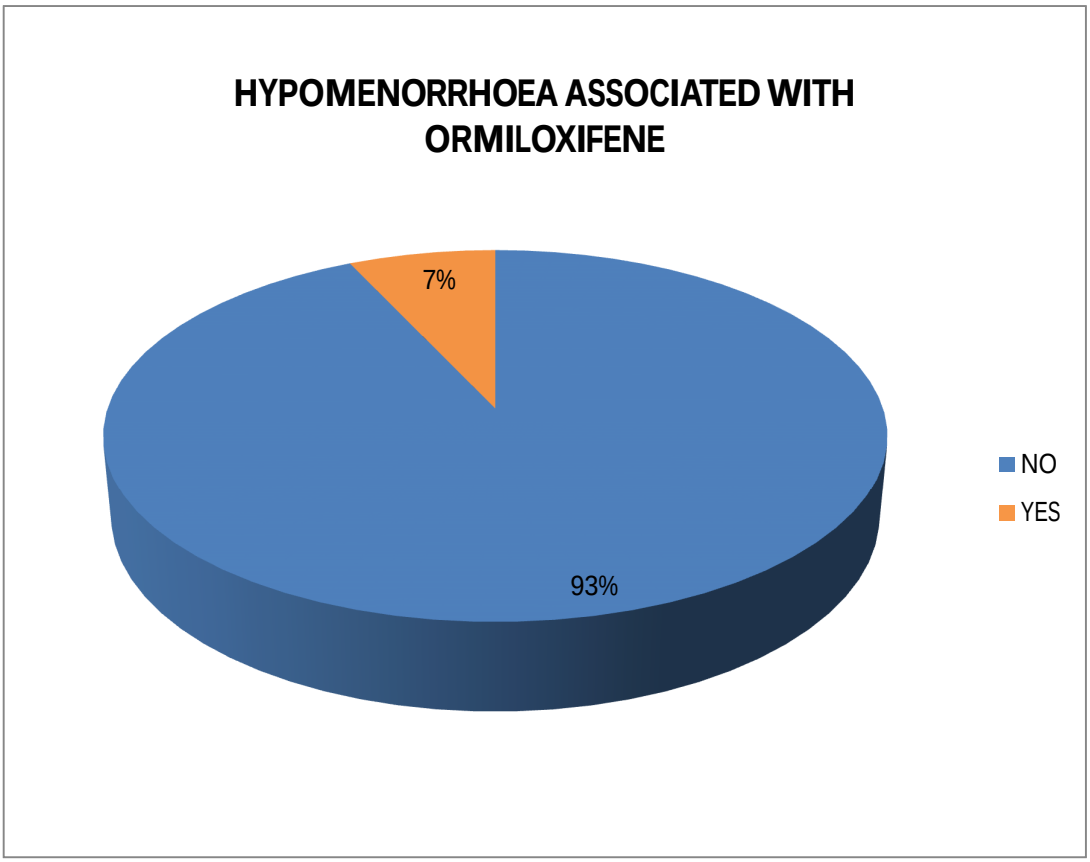
H.AMENORRHOEA WITH ORMILOXEFENE TREATMENT

		Frequency	Percent
Valid	NO	93	93.0
	YES	7	7.0
	Total	100	100.0



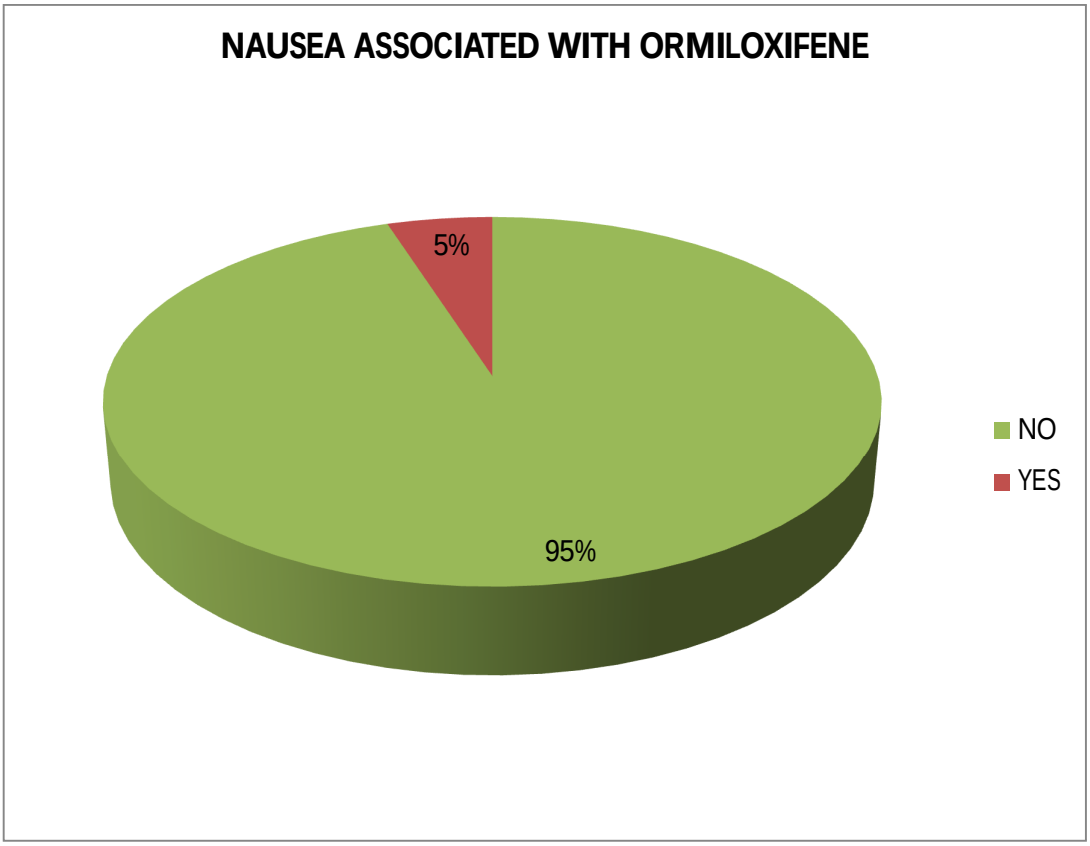
I.HYPOMENORRHOEA WITH ORMILOXEFENE

		Frequency	Percent
Valid	NO	93	93.0
	YES	7	7.0
	Total	100	100.0



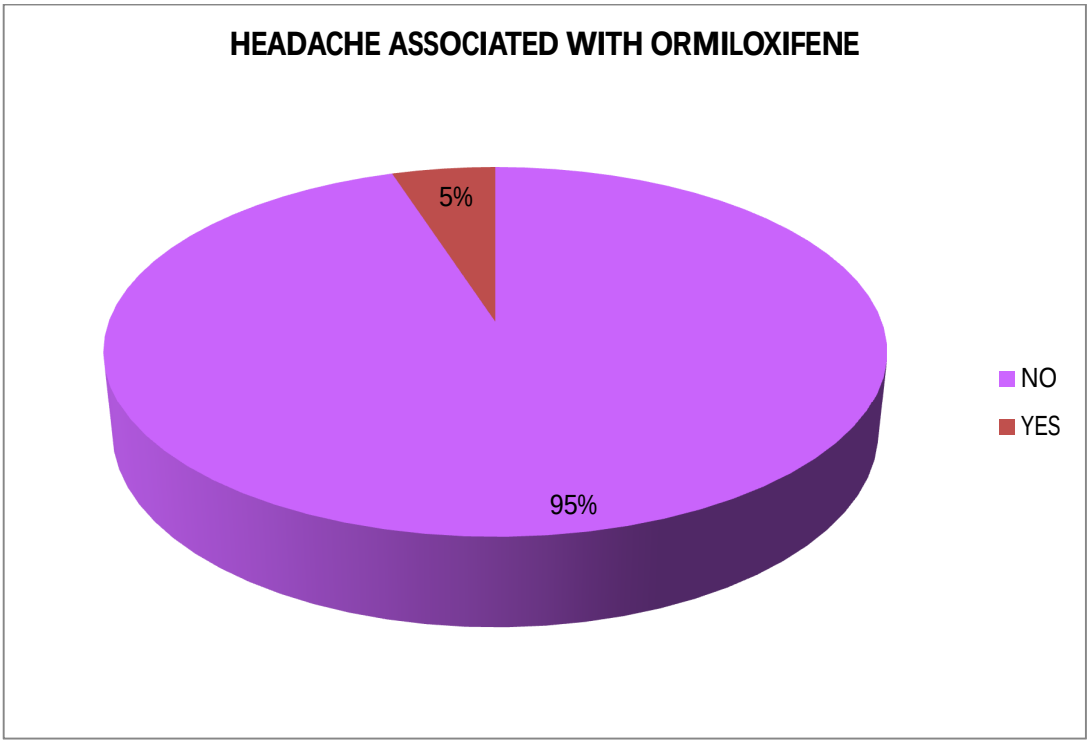
J.NAUSEA ASSOCIATED WITH ORMILOXIFENE

		Frequency	Percent
Valid	NO	95	95.0
	YES	5	5.0
	Total	100	100.0



K.HEADACHE ASSOCIATED WITH ORMILOXIFENE

		Frequency	Percent
Valid	NO	95	95.0
	YES	5	5.0
	Total	100	100.0



Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
AGE	100	31.00	49.00	40.84	4.50302
NO OF DAYS OF FLOW	100	4.00	13.00	7.56	2.08079
CYCLE LENGTH	100	28.00	36.00	31.04	2.13636
DURATION OF COMPLAINT MONTH	100	5.00	18.00	8.92	2.90134
Valid N (listwise)	100				

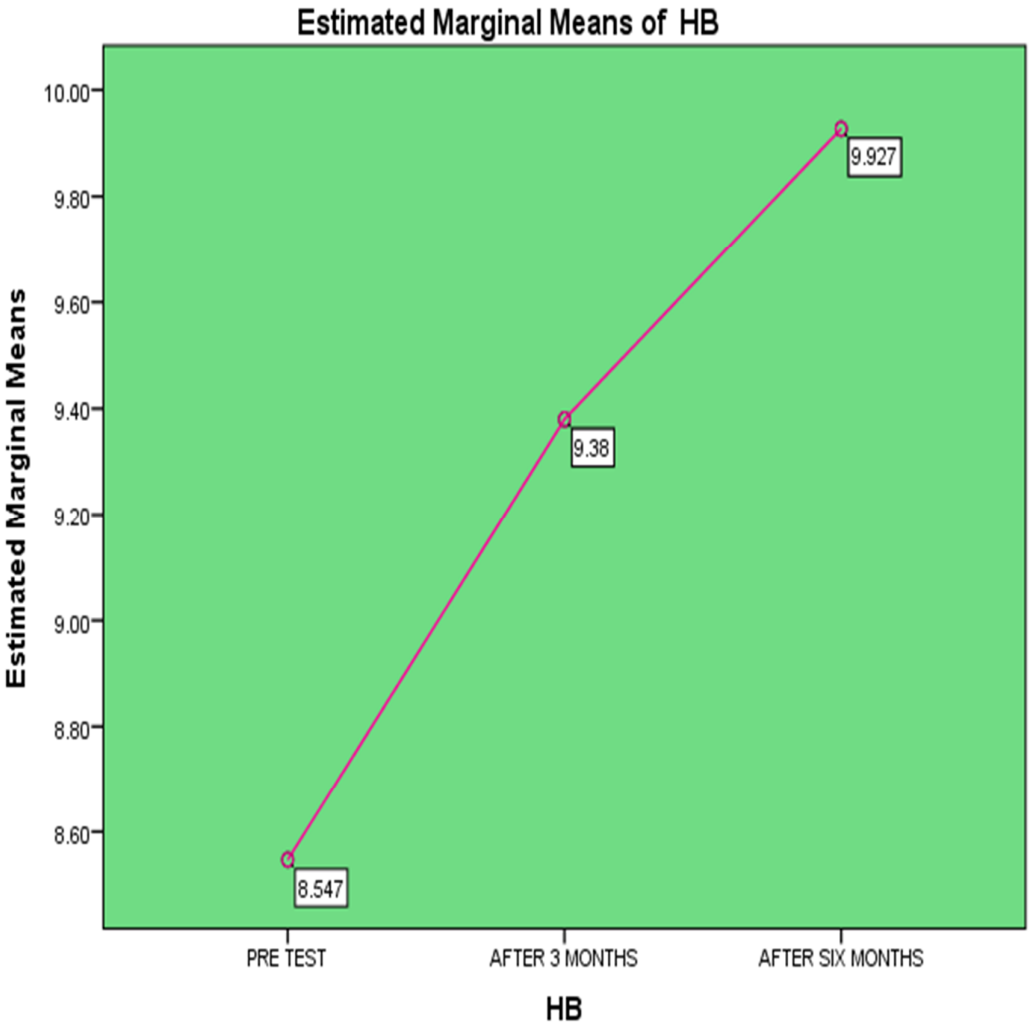
A.COMPARISON OF HB PRETREATMENT AND POSTTREATMENT

Descriptive Statistics

	Mean	**Std. Deviation**	**F**	
HB_0	8.5470	.70760	71.420	P<0.001
HB_3	9.3800	.70022		
HB_6	9.9270	1.62200		

Pairwise Comparisons						
Measure: MEASURE_1						
(I) HB	**(J) HB**	**Mean Difference (I-J)**	**Std. Error**	**Sig.[b]**	**95% Confidence Interval for Difference[b]**	
					Lower Bound	**Upper Bound**
3 PERIOD	1 PERIOD	1.380*	.163	.000	1.056	1.704
	2 PERIOD	.547*	.160	.001	.229	.865

When compared to Pretreatment Hb, Hb value was increased by 1.38gm % at the end of 3 months, and increased by 0.547 gm% at the end of 6 months. Both were significant (p<0.001).


Estimated Marginal Means of HB
Estimated Marginal Means
10.00
9.80
9.60
9.40
9.20
9.00
8.80
8.60
9.927
9.38
8.547
PRE TEST
AFTER 3 MONTHS
AFTER SIX MONTHS
HB

B.COMPARISON OF PBAC PRETREATMENT &

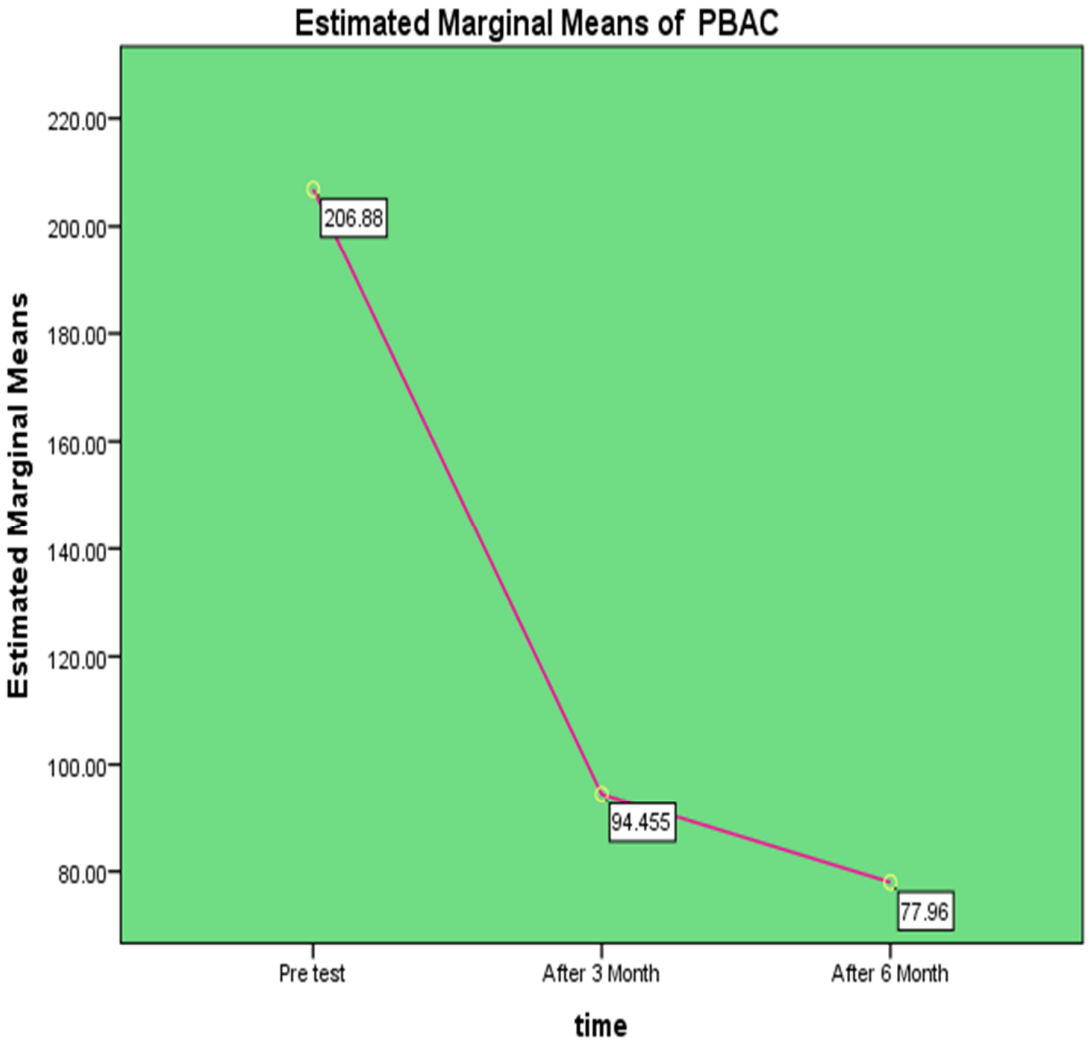
POSTTREATMENT OF ORMILOXIFENE

Descriptive Statistics

	Mean	**Std. Deviation**	
PBAC_0	206.8788	9.40286	F = 2017.391*
PBAC_3	94.4545	19.93729	
PBAC_6	77.9596	27.53955	

PBAC –pictorial blood loss assessment chart

Pairwise Comparisons						
Measure: MEASURE_1						
(I) time	**(J) time**	**Mean Difference (I-J)**	**Std. Error**	**Sig.[b]**	**95% Confidence Interval for Difference[b]**	
					Lower Bound	**Upper Bound**
3	1	-128.919*	2.870	.0001	-135.911	-121.928
	2	-16.495*	2.230	.0001	-21.926	-11.064


Estimated Marginal Means of PBAC
Estimated Marginal Means
220.00
200.00
180.00
160.00
140.00
120.00
100.00
80.00
206.88
94.455
77.96
Pre test
After 3 Month
After 6 Month
time

C.COMPARISON OF ENDOMETRIAL THICKNESS

PRETREATMENT & POSTTREATMENT OF ORMILOXIFENE

Descriptive Statistics

	Mean	Std. Deviation	
ET 0	11.0670	.79558	F= 159.351 *
ET 3	10.1034	.76765	
ET 6	8.9560	1.59806	

Pairwise Comparisons

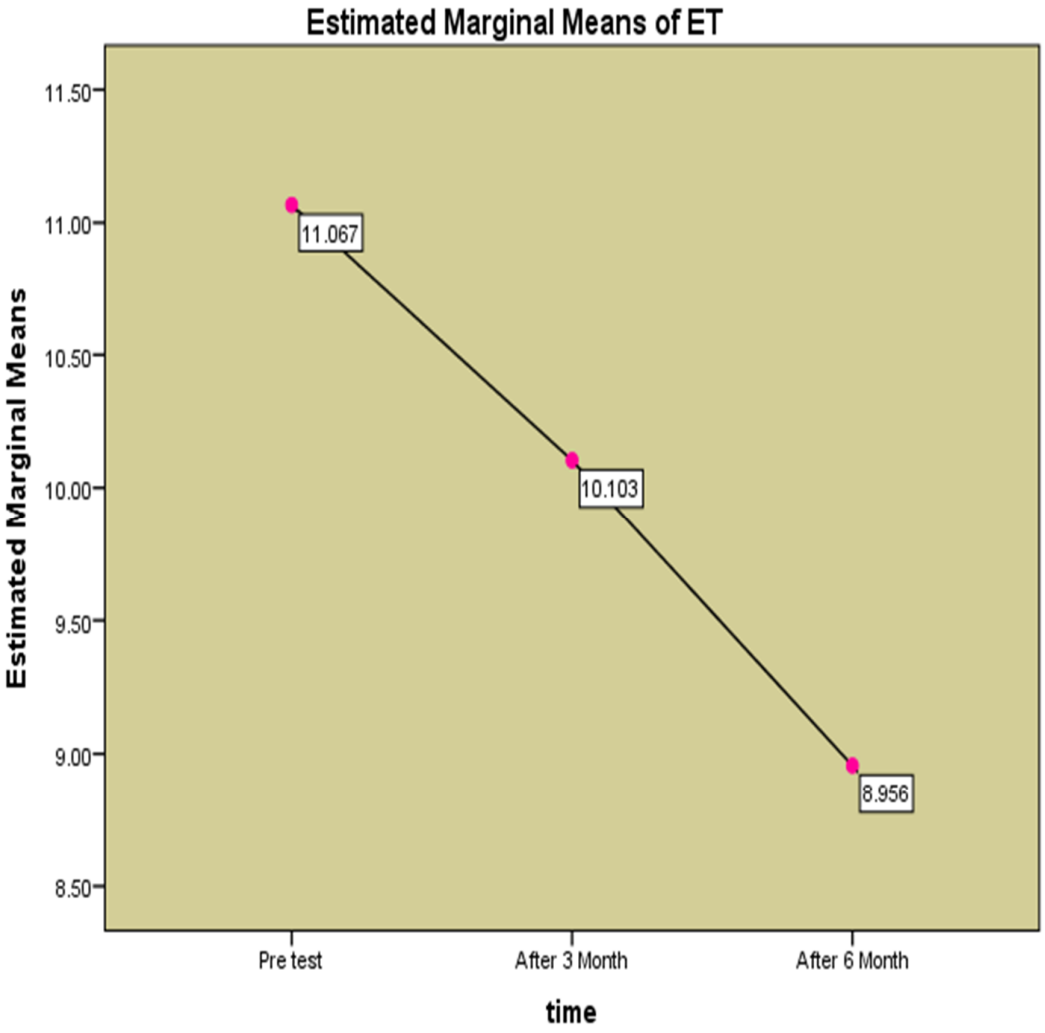
Measure: MEASURE_1

(I) time	(J) time	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
3	1	-2.111*	.167	.000	-2.518	-1.704
	2	-1.147*	.137	.000	-1.480	-.815

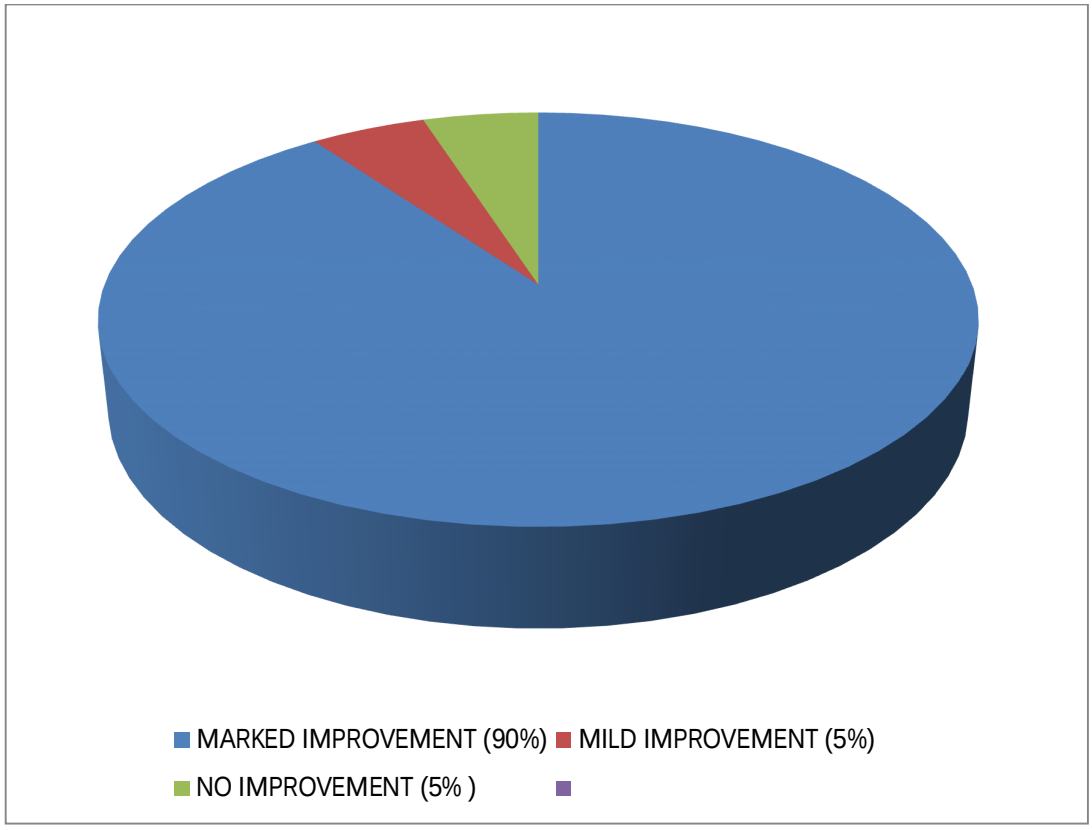
Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.


Estimated Marginal Means of ET
Estimated Marginal Means
11.50
11.00
10.50
10.00
9.50
9.00
8.50
11.067
10.103
8.956
Pre test
After 3 Month
After 6 Month
time

D. TREATMENT OUTCOMES WITH ORMILOXIFENE:



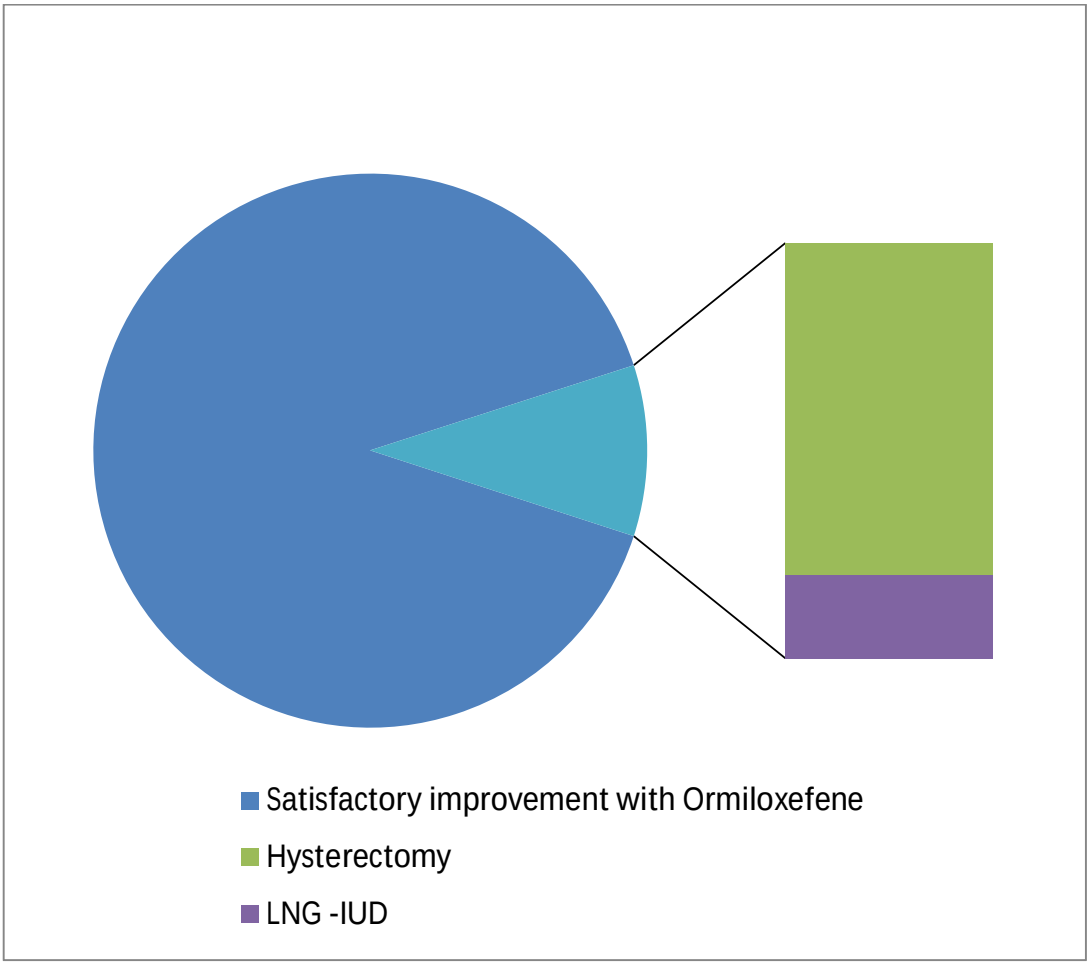
In our study , about 90 % of patients showed marked improvement , while 5 % showed mild improvement and remaining did not respond to ormiloxifene..

D. OVERALL OUTCOME OF TREATED PATIENTS :

In our study out of the total study population 5% showed only mild improvement while 5% didn't respond to treatment.

Out of these 8% of women underwent hysterectomy with the indication being AUB –not responding to medical management. The remaining 2% opted for a trial with Levonorgesterol IUCD.

OVERALL OUTCOME OF TREATED PATIENTS



Discussion

DISCUSSION

Any alteration in bleeding pattern , duration or quantity of menstrual blood flow is regarded as Abnormal Uterine Bleeding . Among the number of hysterectomies done every year about one third is done for perceived alteration in menstrual bleeding. This leads to premature menopause, a debilitatory event in a woman of reproductive age which compromises her cardiovascular , urogenital and even cognitive health. A safe alternative to this is medically managing these menstrual problems thereby preserving the uterus and the ovaries. Drugs used for medical management include hormonal pills, fibrin lysers and specifically developed antagonists to estrogen and progesterone. Among these Ormeloxifene , a site specific estrogen agonist-antagonist has emerged as an effective option and several studies have been conducted to test its efficacy.

In a study conducted by Biswassubhash Chandra et all Ormeloxifene decreased menstrual blood loss by 97.2%($p<0.001$),with a corresponding increase in haemoglobin concentration by 1.31g%. ($p<0.001$, 95 % CI=0.389 to 2.23). USG measurement of endometrium showed a reduction in thickness by 87%.

In an Indian study by Agarwal et al, blood loss as measured by pictorial charts was reduced by 90% ($p < 0.0001$) haemoglobin increased by 0.7g% following 3 months of treatment while 6 monthly values showed a 1.8 g% increase ($p<0.0001$).Endometrial thickness reduced from 11.35 cm to 8.38 cm at

the end of treatment. ($p<0.0001$). 88.3% women showed marked subjective improvement in symptoms.

In an Indian study by the Deepika et al at Manipal university , 9.1% of all gynaecology patients underwent hysterectomy, out of which 39.9 % had Uterine fibroids , 13.9% for uterine prolapsed and about 9.8% for dysfunctional uterine bleeding .In our study after medical management about 8% of study population required hysterectomy , while the remaining 90% improved with Ormiloxifene.

In this study about 100 patients were recruited after meeting the inclusion and exclusion criteria. The mean PBAC score, significantly reduced from 206.8788 to 94.4545 at the end of 3 months and further reduced to 77.9596 at the end of 6 months.($p <0.0001$ significant). On treatment with ormiloxifene , Hb increased by 1.38gm% (mean Hb of 8.5470 gm% to 9.3800 gm%) at the end of 3 months and further improved by 0.547gm % (9.300 gm% to 9.927gm%) at the end of 6 months.

The mean endometrial thickness reduced from 11.0670 mm to 10.1034 mm at the end of 3 months and further reduced to 8.9560 mm at the end of 6 months($p < 0 .05$) . So there was significant reduction in endometrial thickness, PBAC score in patients treated with ormiloxifene along with considerable improvemnt in Hb level thereby improving the quality of life of patints with AUB.

Out of these women about 4 % of women turned up to gynaec op with recurrent heavy menstrual bleeding , who opted for trial with LNG-IUD . So ormiloxifene is cost effective drug in the medical management of AUB with few side effects like hypomenorrhoea , amenorrhoea , headache , nausea and with low recurrence rates . In developing country like India medical management with ormiloxifene can be a safer option thereby reducing the financial burden by limiting the number of hysterectomies and the morbidities associated with surgery.

Conclusion

CONCLUSION

Ormeloxifene, a designer drug significantly reduced the blood loss in patients with AUB evidenced by decrease in PBAC score along with significant rise in haemoglobin levels. Amenorrhea/ hypomenorrhea with the use of ormeloxifene. were desirable side effects in the perimenopausal age group and in women who are unfit for surgery. Further there was a reduction in proportion of patients who underwent hysterectomy in cases treated with ormiloxifene , thereby reducing the morbidities associated with the surgery. It is non-steroidal non-hormonal drug which is metabolically and pharmacologically safe and is protective to both breast and endometrium. The ease of administration of the drug facilitates patient compliance and acceptability and the marked relief of symptoms results in higher satisfaction. Ormeloxifene should be the drug of choice in patients with AUB . It can be used in people who have completed their child bearing but used cautiously after counselling the perimenopausal age group.

Bibliography

BIBLIOGRAPHY

1. Fraser IS, Langham S, Uhl-Hochgraeber K. Health-related quality of life and economic burden of abnormal uterine bleeding. Expert Rev ObstetGynecol 2009;4:179e89.

2. Shapley M, Jordan K, Croft PR. An epidemiological survey of symptoms of menstrual loss in the community. Br J Gen Pract 2004;54:359e63.

3. NICE. Clinical Guideline 44; Heavy menstrual bleeding 2007. National Institute for Health and Clinical Excellence (NICE); Available at: http://www.nice.org.uk/nicemedia/pdf/CG44FullGuideline.pdf.

4. Frick KD, Clark MA, Steinwachs DM, et al. Financial and quality-of-life burden of dysfunctional uterine bleeding among women agreeing to obtain surgical treatment. Womens Health Issues 2009;19:70e8.

5. RCOG. National heavy menstrual bleeding audit second annual report. London: RCOG; 2012.

6. RCOG. National heavy menstrual bleeding audit final report. London: RCOG; 2014.

7. Baird DD, Dunson DB, Hill MC, et al. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J ObstetGynecol 2003;188:100e7.

8. Brahma PK, Martel KM, Christman GM. Future directions in myoma research. ObstetGynecolClin North Am 2006;33: 199e224. xiii.

9. Merrill RM. Hysterectomy surveillance in the United States, 1997 through 2005. Med SciMonit 2008;14:CR24e31.

10. Stewart EA. Uterine fibroids. Lancet 2001;357:293e8.

11. Cardozo ER, Clark AD, Banks NK, et al. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol 2012;206:211.e1e9.

12. Fraser IS, Critchley HO, Broder M, et al. The FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding. SeminReprod Med 2011;29:383e90.

13. Munro MG, Critchley HO, Fraser IS, for the FIGOWorking Group on Menstrual Disorders. The FIGO classification of causes of abnormal uterine bleeding. Int J GynaecolObstet 2011;113:1e2.

14. Wamsteker K, Emanuel MH, de Kruif JH. Transcervicalhysteroscopic resection of submucous fibroids for abnormal uterine bleeding: results regarding the degree of intramural extension. ObstetGynecol 1993;82:736e40.

15. Munro MG. Classification of menstrual bleeding disorders. Rev EndocrMetabDisord 2012;13:225e34.

16. Stewart EA, Nowak RA. Leiomyoma-related bleeding: a classic hypothesis updated for the molecular era. Hum Reprod Update 1996;2:295e306.

17. Doherty L, Mutlu L, Sinclair D, et al. Uterine fibroids: clinical manifestations and contemporary management. ReprodSci 2014;21:1067e92.

18. Sinclair DC, Mastroyannis A, Taylor HS. Leiomyoma simultaneously impair endometrial BMP-2-mediated decidualization and anticoagulant expression through secretion of TGF-beta3. J ClinEndocrinolMetab 2011;96:412e21.

19. Palmer SS, Haynes-Johnson D, Diehl T, et al. Increased expression of stromelysin 3 mRNA in leiomyomas (uterine fibroids) compared with myometrium. J SocGynecolInvestig 1998;5:203e9.

20. Bogusiewicz M, Stryjecka-Zimmer M, Postawski K, et al. Activity of matrix metalloproteinase-2 and -9 and contents of their tissue inhibitors in uterine leiomyoma and corresponding myometrium. GynecolEndocrinol 2007;23:541e6.

21. Wegienka G, Baird DD, Cooper T, et al. Cytokine patterns differ seasonally between women with and without uterine leiomyomata. Am J ReprodImmunol 2013;70:327e35.

22. Dreisler E, Stampe Sorensen S, Ibsen PH, et al. Prevalence of endometrial polyps and abnormal uterine bleeding in a Danish population aged 20-74 years. Ultrasound ObstetGynecol 2009;33:102e8.

23. Preutthipan S, Herabutya Y. Hysteroscopicpolypectomy in 240 premenopausal and postmenopausal women. FertilSteril 2005;83:705e9.

24. Lieng M, Istre O, Sandvik L, et al. Prevalence, 1-year regression rate, and clinical significance of asymptomatic endometrial polyps: cross-sectional study. J Minim Invasive Gynecol 2009;16:465e71.

25. Van den Bosch T, Ameye L, Van Schoubroeck D, et al. Intra-cavitary uterine pathology in women with abnormal uterine bleeding: a prospective study of 1220 women. Facts Views Vis Obgyn 2015;7:17e24.

26. Naftalin J, Hoo W, Pateman K, et al. Is adenomyosis associated with menorrhagia? Hum Reprod 2014;29:473e9.

27. Hulka CA, Hall DA, McCarthy K, et al. Sonographic findings in patients with adenomyosis: can sonography assist in predicting extent of disease? AJR Am J Roentgenol 2002;179:379e83.

28. TandonAnnu M, Goel I, Singh Mati M, Singh Mastan, et al. “The effect of ormeloxifene, a selective estrogen receptor modulator, on the biomarkers of the endometrial receptivity and the pinopode development and its relationship with the fertility and the infertility in Indian subjects” Fertility and Sterility. 2009;91(6):2298–307. [PubMed]

29. Lal J. “Clinical pharmacokinetics and interaction of centchroman—a mini review.” Contraception. 2010;81(4):275–80. [PubMed]

30. Lal J, Nitynand S, Asthana OP, Nagaraja NV, Gupta RC. “The optimization of the contraceptive dosage regimen of centchroman” Contraception. 2001;63(1):47–51. [PubMed]

31. Singh MM. “Centchroman, a selective estrogen receptor modulator, as a contraceptive and for the management of hormone-related clinical disorders” Medicinal Research Reviews. 2001;21(4):302–47. [PubMed]

32. Kriplani A, Kulshrestha V, Agarwal N. “The efficacy and safety of ormeloxifene in the management of menorrhagia: a pilot study” J. Obstet. Gynaecol. 2009;35(4):746–52. [PubMed]

33. Kumar GR, Rituraj K, Hemant BK, Singh MM. The in-vitro anti-cancer breast activity of ormeloxifene is mediated via the induction of apoptosis and autophagy. 37th Annual Conference of the Endocrine Society of India.30 Nov-2 Dec, 2007 Abstract p35.

34. RanjanManisha N, Srivastava Vishal, Sharma Swasti, et al. “Centchroman induces the G0/G1 arrest and the caspase-dependent apoptosis which involves the mitochondrial membrane depolarization in the MCF-7 and the MDA MB-231 human breast cancer cells” Life Sciences. 2008;82:577–90. [PubMed]

35. Porteous A, Prentice A. The medical management of dysfunctional uterine bleeding.Reviews in Gynaecological Practice. 2003;3(2):81–84.

36. Oehler MK, Rees MC. Mennorrhagia : an update. ActaObstetGynecol Scand. 2003;82(5):405–22. [PubMed]

37. Nelson AL, Teal SB. Medical therapies for chronic mennorrhagia. ObstetGynecolSurv. 2007;62(4):272–81. [PubMed]

38. Irvine GA, Cameron IT. The medical management of dysfunctional uterine bleeding.Baillieres Best Pract Res ClinObstetGynaecol. 1999;13(2):189–202. [PubMed]

39. Shelly W, Draper MW, Krishnan V, Wong M, Jaffe RB. The selective estrogen receptor modulators: an update on the recent clinical findings. ObstetGynecolSurv. 2008;63(3):163–81. [PubMed]

40. A. Coulter, J. Kelland, V. Peto, and M.C.P. Rees, Treating menorrhagia in primary care. An overview of drug trials and a survey of prescribing practice, Int J Tech Assess Health Care, 11(3), 1995, 456-471.

41. S. Dadhich, S. Agarwal, M. Soni, and R. Jain, Role of Ormeloxifene in medical management of dysfunctional uterine bleeding, Asian Journal of Obs and Gynae Practice, 6, 2012, 28-31.

42. S.C. Biswas, S.K. Saha, T.S. Bag, S.C. Ghosh Roy, A.C. Roy, and S.P. Kabiraj, Ormeloxifene A Selective Estrogen Receptor Modulator, for treatment of dysfunctional menorrhagia, J ObstetGynecol, 54(1), 2004, 56-59.

43. J.M. Higham, P.M.S. O'Brien, and R.W. Shaw, Assessment of menstrual blood loss using a pictorial chart, Br J ObstetGynaecol, 97, 1990, 734-739.

44. L. Hallberg, and L. Nillsson, Determination of menstrual blood loss, Scand J Clin Lab Invest, 16, 1964, 244-248.

45. A. Kriplani, V. Kulshrestha, and N. Agarwal, Efficacy and safety of ormeloxifene in management of menorrhagia: a pilot study, J ObstetGynaecol Res, 35(4), 2009, 746-752.

46. D. BS, and S.K. Nanda, The role of Sevista in the management of Dysfunctional Uterine Bleeding, J Clin Diagn Res, 7(1), 2013, 132-4. doi: 10.7860/JCDR/2012/4794.2687. Epub 2012 Sep 10.

47. J. Shravage, D. Mekhala, M.B. Bellad, M.S. Ganachari, and H.A. Dhumale, Ormeloxifene versus Medroxyprogesterone Acetate (MPA) in the treatment of Dysfunctional Uterine Bleeding: A double-blind randomized controlled trial, JSAFOG, 3(1), 2011, 21-24.

Annexures

PROFORMA

DATE:

NAME: AGE: LMP:

IP NO:

D.O.A: D.O.D

OBSTETRIC CODE:

ADDRESS :

PRESENTING COMPLAINTS:

MENSTRUAL HISTORY : M/S:

OBSTETRIC HISTORY:

PAST HISTORY:

GENERAL EXAMINATION:

HT: WT: TEMP: PR: BP:

PALLOR: PEDAL EDEMA:

CVS: RS:

P/A:

P/V:

INVESTIGATIONS:

HB: RBS: TFT:

USG:

PRE-TREATMENT :

1. Hb
2. Endometrial thickness
3. PBAC

POST-TREATMENT

3 months

1. Hb
2. Endometrial thickness
3. PBAC

POST-TREATMENT

6 months

1. Hb
2. Endometrial thickness
3. PBAC

MASTER CHART

SI NO	NAME	AGE	OP.NO	PARITY	LMP	NO OF DAYS OF FLOW	CYCLE LENGTH	DURATION OF COMPLAINT (MONTH)	EDUCATION	SOCIO ECONOMIC STATUS	HB 0	ET 0	PBAC 0	HB 3	ET 3	PBAC 3	HB 6	ET 6	PBAC 6	DURATION OF TREATMENT	NO IMPROVEMENT	MILD IMPROVEMENT	MARKED IMPROVEMENT	AMENORRHOEA	HYPOMENORRHOEA	NAUSEA	HEADACHE
1	LAKSHMI	46	266851	2	16/2/16	9	32	8	10	3	9.2	12.1	214	10.1	9.71	90	11.4	8.6	84	6	NO	NO	YES	NO	NO	NO	NO
2	SHANTHI	42	278643	3	14/2/16	6	28	12	10	3	7.8	11.2	208	8.4	9.2	98	10.2	7.3	82	6	NO	NO	YES	NO	NO	NO	NO
3	VASANTHI	37	276543	2	20/2/16	10	30	9	3	4	8.4	12.2	216	9.2	10.42	120	10.8	9.4	96	6	NO	NO	YES	NO	NO	NO	NO
4	SUNDARI	48	216438	2	12/2/2016	7	32	10	8	3	8.8	10.4	210	9.1	8.2	108	10.4	7.2	78	6	NO	NO	YES	NO	NO	NO	NO
5	PONNI	39	219076	4	27/2/16	8	28	14	10	3	9.3	11.6	204	10.1	9.41	102	11.2	7.4	92	6	NO	NO	YES	NO	NO	NO	NO
6	SARALA	36	285095	3	13/2/16	13	30	6	10	4	9.6	12.4	200	10.6	10.3	96	11.4	8.4	32	6	NO	NO	YES	NO	YES	NO	NO
7	MAHALAKSHMI	43	277630	2	3/3/2016	10	35	8	9	3	9.2	12.6	198	9.9	10.4	138	10.4	8.2	114	6	NO	YES	NO	NO	NO	NO	NO
8	MALATHI	47	286103	2	5/3/2016	9	32	10	7	3	8.6	12.2	216	9.6	10.6	86	11.8	7.6	82	6	NO	NO	YES	NO	NO	NO	YES
9	ABIRAMASUNDARI	44	284169	2	27/2/16	7	34	14	10	3	8.8	10.2	218	10.2	8.4	84	12	6.2	87	6	NO	NO	YES	NO	NO	NO	NO
10	SHANTHAKUMARI	38	280940	2	18/2/16	8	29	6	4	4	7.2	12.4	212	8.4	10.2	90	10.6	7.6	80	6	NO	NO	YES	NO	NO	NO	NO
11	LAKSHMI DEVI	39	280965	3	15/2/16	10	32	8	8	3	9.2	12	200	10.2	10.4	86	11.4	9	24	6	NO	NO	YES	YES	NO	NO	NO
12	ANJALA	42	276542	2	21/2/16	5	35	10	5	4	9.8	11.4	202	10.4	10.2	84	11.2	9.3	82	6	NO	NO	YES	NO	NO	NO	NO
13	SELVI	48	298541	2	4/3/2016	9	33	7	10	3	7.6	11	198	8.4	10.2	94	9.8	8.5	95	6	NO	NO	YES	NO	NO	NO	NO
14	SASIKALA	45	228763	3	12/2/2016	7	30	9	10	3	8.2	10.8	196	9.4	9.8	92	10.2	8.2	90	6	NO	NO	YES	NO	NO	YES	NO
15	THENANDAL	40	237609	2	19/2/16	12	35	5	10	3	8.4	12.4	210	8.6	11.8	180	8.4	11.6	145	6	YES	NO	NO	NO	NO	NO	NO
16	DARANI	38	276595	2	4/3/2016	9	34	6	8	3	9.6	11.2	204	10.4	9.7	84	0	0	0	3	NO	NO	NO	NO	NO	NO	NO
17	ANJALI	48	265198	3	20/3/16	7	30	10	8	3	9.2	10.6	198	10.1	9.2	82	11.2	7.4	82	6	NO	NO	YES	NO	NO	NO	NO
18	SANTHA	44	268209	2	26/2/16	7	28	12	ILLITERATE	3	8.6	11.6	206	9.6	10.2	84	10.2	8.8	LAKSHMI	6	NO	NO	YES	NO	NO	NO	NO
19	SUSEELA	42	218709	2	3/2/2016	6	30	8	10	3	8.8	10.8	220	9.9	9.8	90	10.4	8.2	88	6	NO	NO	YES	NO	NO	NO	NO
20	PONNAMAL	46	289463	2	17/2/16	8	32	6	8	3	8	10.6	210	9.2	9.1	96	10	7.9	90	6	NO	NO	YES	NO	NO	NO	NO
21	PAVITHRA	38	289453	2	16/3/16	6	34	10	8	3	8.4	9.4	204	9.6	8.2	86	10.4	7.8	83	6	NO	NO	YES	NO	NO	NO	NO
22	VANAJA	43	276495	2	10/2/2016	6	32	8	5	4	8.6	10.3	198	9.4	9.6	84	10.8	8.2	20	6	NO	NO	YES	YES	NO	NO	NO
23	VASANTHI	38	286407	3	15/2/16	5	36	6	6	4	9.2	10.8	214	10	9.4	122	10.3	8.2	104	6	NO	YES	NO	NO	NO	NO	NO
24	BOMMI	34	278643	2	17/3/16	7	28	12	8	3	8.8	11.4	220	9.6	10.6	94	10.5	9.2	94	6	NO	NO	YES	NO	NO	NO	NO
25	ABIRAMI	47	206543	2	13/3/16	10	34	10	8	3	9.4	11.6	190	10.2	9.8	86	11	8.6	83	6	NO	NO	YES	NO	NO	YES	NO
26	SANKARI	45	239854	4	12/2/2016	9	30	6	9	3	8.8	12.4	198	10	10.2	82	0	0	0	3	NO	NO	NO	NO	NO	NO	NO
27	VARALAKSHMI	36	220918	2	12/3/2016	8	28	8	10	3	9.2	11.8	204	10.4	10.2	84	11.2	9.2	81	6	NO	NO	YES	NO	NO	NO	NO
28	SANGEETHA	38	209534	2	18/3/16	9	34	11	7	3	9.4	12.4	210	10.6	11.2	90	11.2	10	28	6	NO	NO	YES	NO	YES	NO	NO
29	SASI	34	209842	2	22/2/16	6	32	15	6	3	8.8	11.2	210	9.1	11.4	170	9.5	10.9	136	6	YES	NO	NO	NO	NO	NO	NO
30	THIRUMALA	38	269813	2	17/3/16	5	34	8	10	3	9.2	10.6	218	10.4	9.4	84	11.2	8.2	82	6	NO	NO	YES	NO	NO	NO	YES
31	ANANTHI	41	254987	2	12/3/2016	5	30	6	6	3	8.8	9.8	210	9.2	9	90	10.1	8.4	84	6	NO	NO	YES	NO	NO	NO	NO
32	PREMA	45	237698	3	10/2/2016	6	28	15	ILLITERATE	4	9.4	10.6	208	10.2	9.8	86	10.8	8	82	6	NO	NO	YES	NO	NO	NO	NO
33	SUNDARAVALLI	39	228164	3	24/2/16	4	30	6	7	3	7	11.2	214	8.4	9.5	84	9.6	8.6	16	6	NO	NO	YES	YES	NO	NO	NO
34	DHANALAKSHMI	45	220815	2	21/2/16	5	32	10	5	3	8.4	10.8	190	9.2	9.2	98	10.2	8.3	82	6	NO	NO	YES	NO	NO	NO	NO
35	PANDISELVI	48	239069	3	10/2/2016	6	30	8	3	3	9.2	11.4	198	10.1	10.2	96	10.7	9.6	34	6	NO	NO	YES	NO	YES	NO	NO
36	SAMUDEESHWARI	39	231852	2	16/3/16	10	34	9	8	3	8.6	10.2	204	9.9	9.4	84	10.4	9	80	6	NO	NO	YES	NO	NO	NO	NO
37	ANDAL	40	239673	2	9/2/2016	8	29	12	9	3	9	9.6	208	10.3	8.8	96	11	8.3	92	6	NO	NO	YES	NO	NO	NO	NO
38	AMSAVALLI	42	235162	2	2/3/2016	7	30	6	10	3	9.2	10.8	198	10	9.6	128	10.4	8.9	108	6	NO	YES	NO	NO	NO	NO	NO
39	SUNDARI	37	287098	3	3/2/2016	7	32	6	5	3	9.8	12.2	196	10.8	10.4	82	11.8	9.5	76	6	NO	NO	YES	NO	NO	NO	NO
40	PARIMALA	39	216542	2	18/3/16	6	34	8	8	3	8.3	11.7	208	9.4	10.1	96	10.6	9.2	84	6	NO	NO	YES	NO	NO	YES	NO
41	SUSEELA	32	210598	3	17/2/16	10	32	12	8	3	9.2	10.4	206	9.4	9.8	168	9.2	9.6	128	6	YES	NO	NO	NO	NO	NO	NO
42	CHITHRA	36	216566	2	11/2/2016	6	30	6	DEGREE HOLDER	2	9	10.6	218	9.6	9.6	92	10.4	8.8	83	6	NO	NO	YES	NO	NO	NO	YES
43	BARANI	41	228740	4	13/3/16	10	30	10	8	3	8.6	11.2	198	9.9	10.4	83	10.5	9.2	80	6	NO	NO	YES	NO	NO	NO	NO
44	DEVI	39	236509	2	23/2/16	7	35	8	10	3	8	12.5	208	9.2	11.2	95	10	9.4	26	6	NO	NO	YES	NO	YES	NO	NO
45	DESAMANI	47	216590	3	2/3/2016	8	28	9	4	3	9.2	10.6	205	9.8	9.7	103	11.2	8.6	89	6	NO	NO	YES	NO	NO	NO	NO
46	ANNAPOORNI	36	225437	2	1/3/2016	10	32	6	8	3	7.9	11.5	210	8.9	10.3	87	10.1	9.7	82	6	NO	NO	YES	NO	NO	NO	NO
47	LAKSHMI	31	225878	2	23/2/16	10	30	14	10	3	8.3	10.6	214	9.4	9.6	124	9.9	8.9	109	6	NO	YES	NO	NO	NO	NO	NO
48	MAHALAKSHMI	37	229070	2	5/2/2016	8	32	9	9	3	8.8	12.3	190	9.6	11.4	82	10.9	10.3	80	6	NO	NO	YES	NO	NO	NO	NO
49	SARALA	43	216781	3	6/3/2016	6	32	10	8	3	8.4	11.5	212	9	10.6	96	10.3	9.8	86	6	NO	NO	YES	NO	NO	NO	NO
50	USHA	46	227659	2	4/2/2016	5	30	7	5	3	9.3	12.2	206	10.2	11.4	93	11.4	10.3	85	6	NO	NO	YES	NO	NO	NO	NO
51	KAMATCHI	36	226743	2	12/3/2016	8	30	12	4	3	9.6	11.1	215	9.8	10.2	84	10.1	9.9	81	6	NO	NO	YES	NO	NO	NO	NO
52	GOMATHI	32	216542	3	11/2/2016	7	28	10	6	3	8.8	12	200	9.1	11.7	140	9.4	11.5	124	6	YES	NO	NO	NO	NO	NO	NO
53	LAKSHMI	49	234134	2	15/2/16	12	32	6	10	3	8.4	10.3	190	9.6	9.7	87	10.1	9.2	82	6	NO	NO	YES	NO	NO	NO	NO

54	PANJALAI	43	226589	2	12/3/2016	9	30	8	8	3	9	11.3	207	10.1	10.2	89	10.8	9.8	84	6	NO	NO	YES	NO	NO	NO	YES
55	SUNDARAVADUVU	45	235416	2	2/2/2016	6	28	12	8	3	7.2	10.2	210	8.8	9.8	84	9.2	9	83	6	NO	NO	YES	NO	NO	NO	NO
56	SHENBAGAM	38	229073	2	10/1/2016	5	29	18	6	3	9.1	11.2	213	9.9	10.6	82	10.2	9.9	18	6	NO	NO	YES	YES	NO	NO	NO
57	BANUMATHI	35	225074	2	1/3/2016	10	32	6	8	3	8.4	10.2	218	9.6	9.8	89	10.1	9.2	82	6	NO	NO	YES	NO	NO	NO	NO
58	CHELLAMMAL	48	237619	2	14/2/16	8	30	6	10	3	7.5	9.7	198	8.8	9	79	9.2	8.7	75	6	NO	NO	YES	NO	NO	YES	NO
59	SELVI	37	227612	2	10/2/2016	5	30	10	9	3	8	10.3	216	9.1	9.7	84	9.9	9.1	81	6	NO	NO	YES	NO	NO	NO	NO
60	MALALAKSHMI	34	220060	2	15/2/16	7	34	8	6	3	8.5	11.1	218	9.4	10.4	128	9.8	9.8	112	6	NO	YES	NO	NO	NO	NO	NO
61	ANJALA	47	225671	4	21/1/16	6	29	9	5	3	9.2	12.2	208	9.8	11.4	86	10.4	10.9	81	6	NO	NO	YES	NO	NO	NO	NO
62	KUMARI	32	228164	2	2/2/2016	9	28	10	7	3	8.6	10	219	9.3	9.6	83	9.8	8.9	78	6	NO	NO	YES	NO	NO	NO	NO
63	AMBIKA	45	220945	2	31/1/16	7	30	5	9	3	9.4	10.2	215	10.1	9.8	88	10.5	9	82	6	NO	NO	YES	NO	NO	NO	NO
64	YASMIN	40	236571	2	14/2/16	5	32	9	5	3	8.2	11.4	190	9.3	10.9	85	9.9	10	36	6	NO	NO	YES	NO	YES	NO	NO
65	SHEELA	43	212565	2	1/3/2016	9	34	10	8	3	8.5	11.2	197	9.3	10.9	82	10.2	9.8	78	6	NO	NO	YES	NO	NO	NO	NO
66	DURGADEVI	47	218954	2	17/2/16	7	32	8	10	3	8.1	10.2	193	8.5	9.9	144	8.9	9.6	119	6	YES	NO	NO	NO	NO	NO	NO
67	ELLAMMAL	46	225673	3	11/2/2016	7	30	6	6	3	7	11.3	209	8.2	10.8	78	9.3	9.9	74	6	NO	NO	YES	NO	NO	NO	NO
68	SWARAM	39	212564	2	6/2/2016	5	28	5	7	3	7.2	10.5	217	8	9.8	82	9.1	9	78	6	NO	NO	YES	NO	NO	NO	NO
69	RAJALAKSHMI	47	225683	2	18/2/16	8	28	14	9	3	8.3	11.2	219	9.1	10.8	84	10.2	10	12	6	NO	NO	YES	YES	NO	NO	NO
70	ROSY	39	220435	2	11/2/2016	11	30	8	10	3	8.6	10.9	216	9.2	9.9	88	9.8	9.2	84	6	NO	NO	YES	NO	NO	NO	NO
71	HEMA	36	225423	2	16/1/16	6	31	6	6	3	7.3	9.9	210	8.4	9	82	9.2	8.7	79	6	NO	NO	YES	NO	NO	NO	NO
72	THIRUPPAMMA	45	217837	3	12/2/2016	8	34	8	8	3	8.2	10.2	196	9.1	9.8	84	9.8	9.2	81	6	NO	NO	YES	NO	NO	YES	NO
73	RAJESHWARI	42	229037	3	18/2/16	12	30	6	10	3	8.6	10.5	219	9.2	9.8	78	9.6	9	75	6	NO	NO	YES	NO	NO	NO	NO
74	FATHIMA	38	226190	2	10/2/2016	9	31	10	4	3	7.5	11.2	210	8.6	10.9	89	9.2	10.1	84	6	NO	NO	YES	NO	NO	NO	NO
75	GRACY	36	236254	2	19/2/16	5	35	8	7	3	8.3	12.1	197	8.8	11.4	94	9.3	10.8	88	6	NO	NO	YES	NO	NO	NO	NO
76	JAYANTHI	41	236803	2	15/2/16	8	32	5	9	3	7.8	10.4	217	8.6	9.9	91	9.1	8.9	89	6	NO	NO	YES	NO	NO	NO	NO
77	MEENAMMAL	45	238715	2	3/3/2016	4	30	7	6	3	9.2	11.3	210	10.1	10.9	84	10.5	9.9	81	6	NO	NO	YES	NO	NO	NO	NO
78	KALAIVANI	42	229192	2	23/2/16	9	29	12	10	3	8.3	10.9	197	9.4	9.9	87	10.2	8.8	43	6	NO	NO	YES	NO	YES	NO	NO
79	PREMALATHA	39	227145	2	18/2/16	13	30	10	5	3	8.2	11.3	219	9	10.8	95	10.1	9.9	89	6	NO	NO	YES	NO	NO	NO	NO
80	ARASI	42	229063	2	1/3/2016	8	32	6	8	3	7.6	10.2	210	8.8	9.8	98	9.2	8.8	89	6	NO	NO	YES	NO	NO	NO	NO
81	LAKSHMIDEVI	46	225671	2	20/2/16	5	30	8	9	4	8.4	12.1	216	9	11.9	146	8.8	11.6	138	6	YES	NO	NO	NO	NO	NO	NO
82	GAYATHRI	38	226753	2	14/2/16	8	32	14	9	3	8.8	10.5	212	9.3	9.9	88	9.5	8.7	82	6	NO	NO	YES	NO	NO	NO	NO
83	NEELA	39	215643	2	17/2/16	5	29	9	8	3	7.6	11.6	218	8.2	10.2	93	9.2	9.9	24	6	NO	NO	YES	YES	NO	NO	NO
84	REKHA	40	224312	3	1/3/2016	9	32	6	9	3	9.2	10.2	190	10.1	9.8	87	10.8	9	83	6	NO	NO	YES	NO	NO	NO	NO
85	UNAMALAI	47	216578	4	7/2/2016	12	34	9	10	3	9.3	11.3	219	10.2	10.7	84	10.6	10.1	81	6	NO	NO	YES	NO	NO	NO	NO
86	ILLAMALLI	39	228162	2	9/2/2016	7	32	10	6	3	8.4	12.2	215	9.2	11.7	92	9.8	10.9	89	6	NO	NO	YES	NO	NO	NO	NO
87	PAVITHRADEVI	37	226547	2	26/1/16	9	30	5	8	3	8.8	10.1	210	9.3	9.5	94	9.9	8.9	82	6	NO	NO	YES	NO	NO	NO	NO
88	VASANTHI	35	220567	2	21/2/16	5	30	6	10	3	9.4	11.3	190	9.9	10.6	87	10.2	9.9	84	6	NO	NO	YES	NO	NO	NO	NO
89	THANGAM	46	220745	3	15/2/16	9	28	16	7	3	7	10.3	197	7.8	9.9	84	8.8	9	79	6	NO	NO	YES	NO	NO	NO	NO
90	CHITHRADEVI	38	231567	2	1/3/2016	5	31	18	6	3	7.2	10.2	195	8.1	9.6	82	9	8.9	78	6	NO	NO	YES	NO	NO	NO	YES
91	NESAMANI	42	226783	2	21/2/16	6	30	6	4	3	6.8	11.7	190	7.4	10.6	78	8.3	9.9	75	6	NO	NO	YES	NO	NO	NO	NO
92	KALPANA	38	231452	2	16/3/16	6	32	8	9	3	8.6	10.5	210	8.8	9.9	83	9.1	8.9	79	6	NO	NO	YES	NO	NO	NO	NO
93	BAGHYALAKSHMI	45	229647	2	27/2/16	5	29	10	6	3	8.8	11.6	219	9.2	10.5	84	9.8	9.7	81	6	NO	NO	YES	NO	NO	NO	NO
94	SUNDARAVADIVU	35	228945	2	2/2/2016	9	34	6	8	3	9.1	10.2	220	9.4	9.7	79	9.9	8.9	45	6	NO	NO	YES	YES	NO	NO	NO
95	MUTHU	48	227843	2	16/2/116	7	28	8	4	3	7.6	11.3	214	8.2	10.5	85	9	9.6	82	6	NO	NO	YES	NO	NO	NO	NO
96	NAGALAKSHMI	38	229835	3	10/2/2016	6	32	10	7	3	8.2	10.3	219	8.8	9.9	83	9.3	8.6	79	6	NO	NO	YES	NO	NO	NO	NO
97	OORVASI	45	227690	2	14/2/16	6	34	7	10	3	9	9.9	205	9.4	9.3	84	9.9	8.9	38	6	NO	NO	YES	NO	YES	NO	NO
98	XAVIER MARY	36	231467	2	16/3/16	5	30	12	6	3	8.4	10.1	201	9.1	9.5	91	9.8	8.4	89	6	NO	NO	YES	NO	NO	NO	NO
99	SHANTHA	40	231376	2	1/3/2016	8	28	8	9	4	7.8	11.4	180	8.2	10.6	86	9.2	9.6	82	6	NO	NO	YES	NO	NO	NO	NO
100	VENNILA	38	224523	2	16/2/16	9	30	9	5	3	9.2	12.1	207	9.8	11.7	88	10.1	10.2	86	6	NO	NO	YES	NO	NO	NO	NO

MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.A.Kanimozhi
PG in M.S.(O & G)
Madras Medical College/KGH
Chennai 600 003

Dear Dr.A.Kanimozhi,

The Institutional Ethics Committee has considered your request and approved your study titled **" TO STUDY THE EFFICACY OF ORMILOXIFENE IN THE MEDICAL MANAGEMENT OF DYSFUNCTIONAL UTERINE BLEEDING " - NO.19012016.**

The following members of Ethics Committee were present in the meeting hold on **12.01.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.R.Vimala,MD.,Dean,MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD.,Inst.of Pharmacology,MMC,Ch-3	: Member
5.Prof.P.Raghumani,MS, Dept.of Surgery,RGGGH,Ch-3	: Member
6.Prof.M.Saraswathi,MD.,Director, Inst.of Path,MMC,Ch-3	: Member
7.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
8.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
9.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE

MADRAS MEDICAL COLLEGE
21 JAN 2016
CHENNAI-600 003

INFORMATION SHEET

We are conducting a study on"**To study the efficacy of ormiloxifene in the medical management of Dysfunctional Uterine Bleeding** " among patients attending Kasturba Gandhi Government Hospital Chennai and for that your clinical details may be valuable to us.

- We are selecting certain patients and if you are found eligible, we may be using your clinical details in such a way so as to not affect your final report or management.
- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.
- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.
- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator Signature of participant

Date: Date:

ஆராய்ச்சி தகவல் தாள்

”மாதவிடாய் சுழற்சி பிறழ்ச்சி உள்ள பெண்களுக்கு அறுவை சிகிச்சை அல்லாது ஆர்மிளாசிபின் மாத்திரையின் மூலம் சரிசெய்தல் பற்றிய ஆய்வு.

ஆய்வின் நோக்கம்:
மாதவிடாய் சுழற்சி பிறழ்ச்சி உள்ள பெண்களுக்கு அறுவை சிகிச்சை அல்லாது ஆர்மிளாசிபின் மாத்திரையின் மூலம் உதிரப்போக்கை கட்டுப்படுத்துதல். இரத்தத்தில் ஹிமோகுளோபின் அளவை அதிகரித்தல், கர்ப்பப்பை உள்ஜவ்வின் தடிமனை குறைத்தல் என்பதே இந்த ஆய்வின் நோக்கம்.

ஆய்வின் செயல்முறை:
35 வயதிற்கு மேற்பட்ட மாதவிடாய் சுழற்சி பிறழ்ச்சி உள்ள பெண்கள் ஆய்வுக்கு தேர்ந்தெடுக்கப்படுவர். அவர்களுக்கு தைராய்டு, சிறுநீரகம் மற்றும் கல்லீரல் செயல்பாடு, இரத்தம் உறைதலில் ஏதேனும் குறைபாடுகள், மற்றும் கர்ப்பப்பைக் கட்டி உள்ளிட்ட குறைபாடுகள் இல்லை என்று உறுதி செய்யப்படும்.
பின்னர் அவர்களுக்கு ஆர்மிளாசிபின் என்னும் மாத்திரையை வாரத்திற்கு இரண்டு முறை என்று பன்னிரெண்டு வாரத்திற்கும் பின்னர் வாரத்திற்கு ஒரு முறை என்று பன்னிரெண்டு வாரத்திற்கும் கொடுத்து அதன் மூலம் உதிரபோக்கு குறைதல், இரத்தத்தில் ஹிமோகுளோபின் அளவு அதிகரித்தல், கர்ப்பப்பை உள்ஜவ்வின் தடிமனை குறைதல் ஆகியவை கண்காணிக்கப்படும்.

ஆய்வினால் ஏற்படும் நன்மைகள்:
இதன் மூலம் மாதவிடாய் சுழற்சி பிறழ்ச்சி உள்ள பெண்களுக்கு அறுவை சிகிச்சை அல்லாது மாத்திரையின் மூலம் சரிசெய்ய வாய்ப்பு ஏற்படும்.

மருத்துவ சிகிச்சையின் தகவல்கள் குறித்த விபரங்கள்:
உங்கள் மருத்துவ சிகிச்சை பற்றிய தகவல்கள் இரகசியமாக பாதுகாக்கப்படும்.
நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களுக்கு பரிசோதனைகள் செய்து அதன் தகவல்களை ஆராய்வோம். அதனால் தங்கள் நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக் கொள்கிறோம். முடிவுகள் அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்கள் பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதை தெரிவித்துக் கொள்கிறோம்.
இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களது விருப்பத்தின் பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.
இந்த சிறப்பு சிகிச்சையின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சி முடிவின்போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி: இடம்:

CONSENT FORM

STUDY TITLE :

"To study the efficacy of ormiloxifene in the medical management of Dysfunctional Uterine Bleeding"

STUDY CENTRE :Institute of Social Obstetrics and Govt. KGH,Chennai.

PARTICIPANT NAME :

AGE: **SEX:** **J.D.NO.**

I confirm that I have understood the purpose of procedure for the above study, I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the possible complications that may occur during the procedure, I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason.

I understand that investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties of published, unless as required under the law. I agree not to restrict the use of any or results that arise from the study.

I hereby consent to participate in this **"To study the efficacy of ormiloxifene in the medical management of Dysfunctional Uterine Bleeding"**

Signature of Investigator: Place :

Date :

Study Investigators Name: Institution:

Signature / Thumb Impression

Thanking you,

Yours faithfully,

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு:

மாதவிடாய் சுழற்சி பிறழ்ச்சி உள்ள பெண்களுக்கு அறுவை சிகிச்சை அல்லாது ஆர்மிளாசிபின் மாத்திரையின் மூலம் சரிசெய்தல் பற்றிய ஆய்வு.

ஆய்வு நடத்தப்படும் இடம்:

அரசு கஸ்தூரி பாய் காந்தி தாய் சேய் நல மருத்துவமனை மற்றும் சமூக மகப்பேறுயியல் மையம்

பங்கு பெறுபவரின் பெயர்: பங்கு பெறுபவரின் வயது:

பங்கு பெறுபவரின் எண்:

இந்த ஆய்வில் குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. நான் இவ்வாய்வில் தன்னிச்சையாக பங்கேற்கிறேன் எந்த காரணத்தினாலோ எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக் கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ அதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என்பதை அறிந்து கொள்கிறேன். இந்த ஆய்வின் மூலம் கிடைக்கும் முடிவை பயன்படுத்திக் கொள்ள மறுக்கமாட்டேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன்.

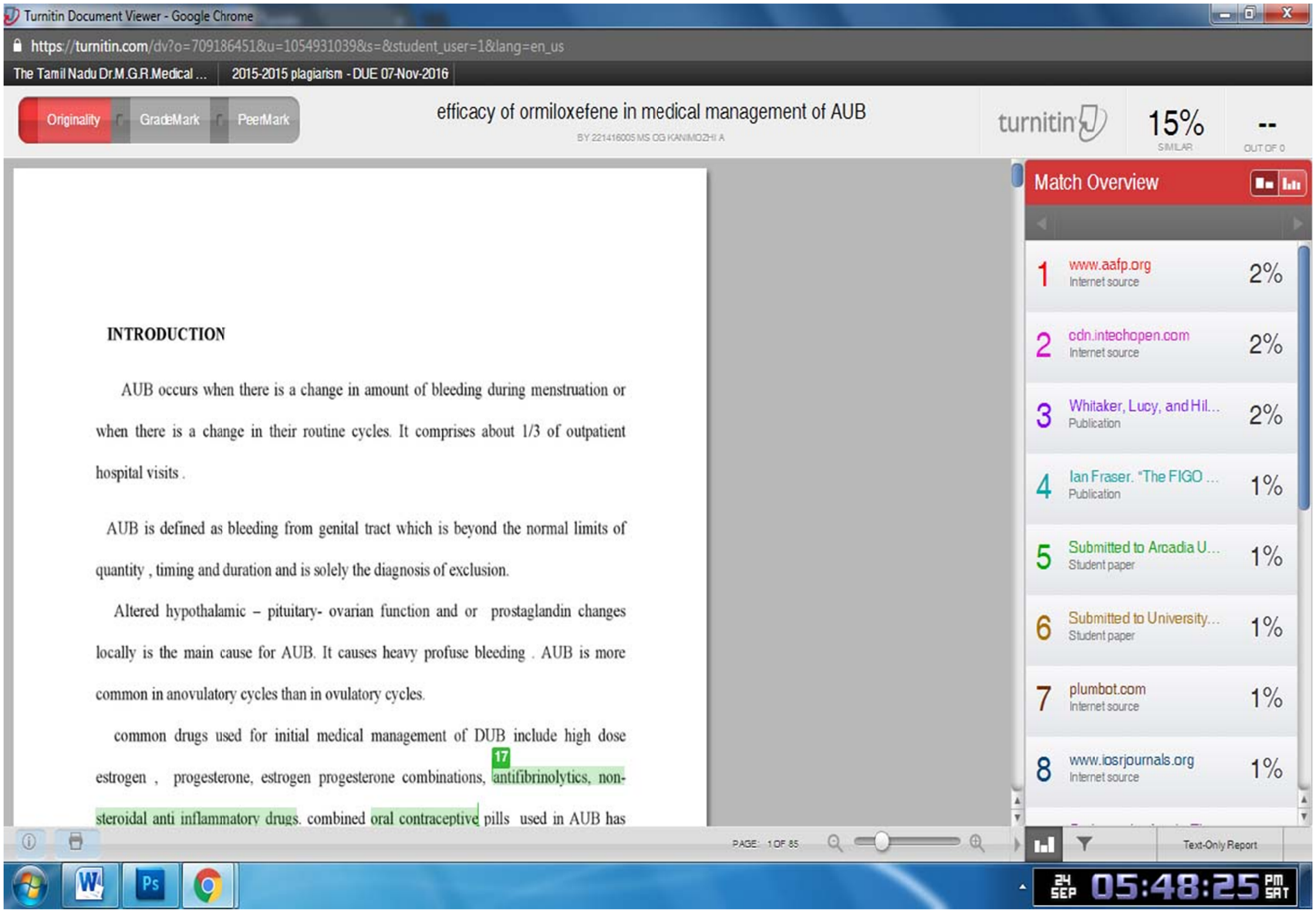
பங்கேற்பவரின் கையொப்பம்
இடம்:
தேதி:

சாட்சிகளின் கையொப்பம்
இடம்:
தேதி:

பங்கேற்பவரின் பெயர் மற்றும் விலாசம்

ஆய்வாளரின் கையொப்பம்

இடம் தேதி:

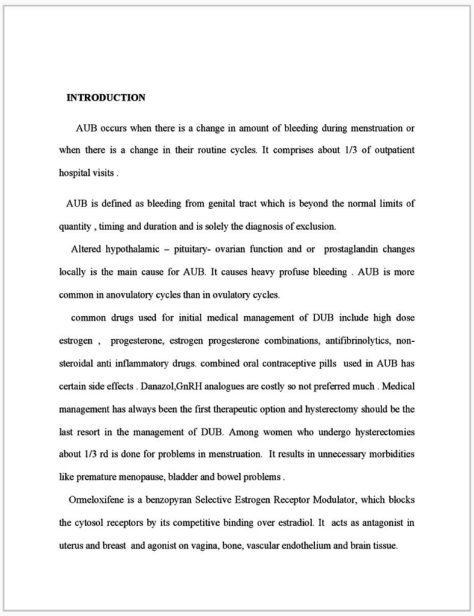

Turnitin Document Viewer - Google Chrome
https://turnitin.com/dv?o=709186451&u=1054931039&s=&student_user=1&lang=en_us
The Tamil Nadu Dr.M.G.R.Medical ...
2015-2015 plagiarism - DUE 07-Nov-2016
Originality
GradeMark
PeerMark
efficacy of ormiloxefene in medical management of AUB
BY 221416005 MS OG KANIMOZHI A
turnitin
15%
SIMILAR
--
OUT OF 0
INTRODUCTION
AUB occurs when there is a change in amount of bleeding during menstruation or when there is a change in their routine cycles. It comprises about 1/3 of outpatient hospital visits .
AUB is defined as bleeding from genital tract which is beyond the normal limits of quantity , timing and duration and is solely the diagnosis of exclusion.
Altered hypothalamic – pituitary- ovarian function and or prostaglandin changes locally is the main cause for AUB. It causes heavy profuse bleeding . AUB is more common in anovulatory cycles than in ovulatory cycles.
common drugs used for initial medical management of DUB include high dose estrogen , progesterone, estrogen progesterone combinations, antifibrinolytics, non-steroidal anti inflammatory drugs. combined oral contraceptive pills used in AUB has
Match Overview
1 www.aafp.org Internet source 2%
2 cdn.intechopen.com Internet source 2%
3 Whitaker, Lucy, and Hil... Publication 2%
4 Ian Fraser. "The FIGO ... Publication 1%
5 Submitted to Arcadia U... Student paper 1%
6 Submitted to University... Student paper 1%
7 plumbot.com Internet source 1%
8 www.iosrjournals.org Internet source 1%
PAGE: 1 OF 85
Text-Only Report
24 SEP 05:48:25 PM SAT

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	221416005 Ms Og KANIMOZHI A
Assignment title:	2015-2015 plagiarism
Submission title:	efficacy of ormiloxefene in medica...
File name:	last_edit.docx
File size:	593.5K
Page count:	85
Word count:	6,031
Character count:	36,162
Submission date:	23-Sep-2016 03:02PM
Submission ID:	709186451



INTRODUCTION

AUB occurs when there is a change in amount of bleeding during menstruation or when there is a change in their routine cycles. It comprises about 1/3 of outpatient hospital visits .

AUB is defined as bleeding from genital tract which is beyond the normal limits of quantity , timing and duration and is solely the diagnosis of exclusion.

Altered hypothalamic – pituitary- ovarian function and or prostaglandin changes locally is the main cause for AUB. It causes heavy profuse bleeding . AUB is more common in anovulatory cycles than in ovulatory cycles.

common drugs used for initial medical management of DUB include high dose estrogen , progesterone, estrogen progesterone combinations, antifibrinolytics, non-steroidal anti inflammatory drugs. combined oral contraceptive pills used in AUB has certain side effects . Danazol,GnRH analogues are costly so not preferred much . Medical management has always been the first therapeutic option and hysterectomy should be the last resort in the management of DUB. Among women who undergo hysterectomies about 1/3 rd is done for problems in menstruation. It results in unnecessary morbidities like premature menopause, bladder and bowel problems .

Ormeloxifene is a benzopyran Selective Estrogen Receptor Modulator, which blocks the cytosol receptors by its competitive binding over estradiol. It acts as antagonist in uterus and breast and agonist on vagina, bone, vascular endothelium and brain tissue.